

**ASYMMETRIC HYDROGENATIONS OF CHIRAL ACYCLIC ALKENES FOR
IMPORTANT CHIRON SYNTHESSES**

A Dissertation

by

YE ZHU

Submitted to the Office of Graduate Studies of
Texas A&M University
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

May 2011

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Approved by:

Chair of Committee,	Kevin Burgess
Committee Members,	John Gladysz
	Brian Connell
	Rayford G. Anthony
Head of Department,	David Russell

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ABSTRACT

Asymmetric Hydrogenations of Chiral Acyclic Alkenes for Important Chiron Syntheses.

(May 2011)

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Chair of Advisory Committee: Dr. Kevin Burgess

Hydrogenation of "largely unfunctionalized" alkenes has been an active area of research for about a decade. Many catalysts have been prepared but we noticed that comparatively few substrates have been studied and none of these hydrogenations provided useful chirons for the organic synthesis area. That motivated us to investigate asymmetric hydrogenations of chiral acyclic alkenes, which are seldom used for hydrogenations and usually the reactions are fully substrate controlled. It emerged that such reactions could provide a concise entry points into chirons that can be used to prepare many natural products.

Asymmetric hydrogenations of functionalized, but not coordinatively functionalized, alkenes have been used to prepare several chirons for syntheses of polyketide natural products using our *N*,carbene Crabtree's catalyst analog. Starting from optically active starting materials (eg Roche esters, lactic acid, glyceraldehyde dimethyl ketals, amino acids), highly optically active chiral alkenes can be made in several steps with high yield. With the iridium catalyzed asymmetric hydrogenations, chiral ethers, *1,3-hydroxymethyl* chiron, *α-methyl-β-hydroxy-γ-methyl* chiron, *α-methyl-γ-alkyl-γ-amino acid* can be obtained with high stereoselectivities. With those well-developed methodologies, (-)-dihydromyoporone, (-)-spongidepsin, (-)-invictolide have been prepared with high efficiency.

Not like the vinyl acetate, which can be hydrogenated quite well with many Rh catalysts, the alkyl vinyl ether does not have a coordination functional group nearby, hence it is a difficult substrate for asymmetric hydrogenation and there are relatively few

reports. Also the simple alkyl enol ether is quite acid sensitive and the Pfaltz's type *N,P*-Ir catalysts cannot hydrogenate the simple alkyl enol ethers well under the standard hydrogenation conditions. We explored many alkyl enol ethers and found some of them can be hydrogenated efficiently (50 bar H₂, 1 mol % *N,carbene*-Ir catalyst, 25 °C) with high enantioselectivities (up to 98% *ee*). This study led us to suspect that more protons were produced when *N,P*-Ir catalyst precursors were used relative to the corresponding carbene catalyst since the former only gave *complex mixture* when being used. DFT calculations and several other experiments supported this postulation.

DEDICATION

To

my wife, Wenjun Wei

and

my parent, Gang Zhu and Wangyu Huang,

and

my sister Ling Zhu

ACKNOWLEDGEMENTS

I thank Prof. Kevin Burgess for all the guidance and support he gave me during my graduate study at Texas A&M University. I am really lucky to have had such a good Ph.D. advisor.

I thank Prof. Brian Connell for all the classes taught and support during my graduate study. He is one of the best teachers that I have ever met.

I thank Prof. John Gladysz for the encouragement at my oral prelim exams, which inspired me to work harder in my remaining years of studies.

I thank Prof. Rayford G. Anthony for spending time on my Ph.D. defense.

I thank Dr. Yubo Fan and Dr. Aurore Loudet for the excellent collaboration work!

I thank Mrs. Jill Powers and Miss Whitney Ajie for their assistance through out all these years.

I thank my wife, Wenjun, my parents and my sister for their love, patience and support.

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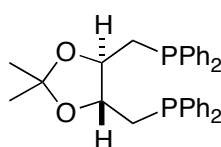
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CHAPTER I

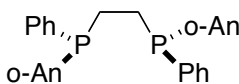
INTRODUCTION

1.1 Chiral iridium homogeneous hydrogenation catalysts

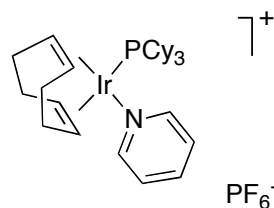
Transition metal catalyzed homogeneous enantioselective hydrogenations emerged in the 1960s.^{1,2} Since then numerous chiral hydrogenation catalysts have been synthesized and many functionalized substrates can be hydrogenated in good enantiomeric excess and yields.³⁻⁶ This breakthrough is largely due to the findings that good hydrogenation stereoselectivity might result from C_2 -symmetric diphosphine ligands such as DIOP⁷ and DIPAMP⁸. Since that time, numerous other phosphorus ligands have been introduced,³ and hence have considerably expanded the scope of enantioselective hydrogenations.



(-)-DIOP



(R,R)-DIPAMP



Crabtree's catalyst

Review of the extensive and fundamentally important research on Rh-, Ir-, Ru-diphosphine complexes³⁻⁶ may create the impression that stereoselective hydrogenations of alkenes is a solved problem. In fact, metal diphosphine complexes do not hydrogenate tri- or tetra-substituted alkenes at useful rates unless the substrate has one or more coordinating functional groups (CFGs) to anchor the substrate to the metal so facilitating catalysis.^{9,10} Asymmetric hydrogenations mediated by Rh-, Ir-, Ru-diphosphine complexes are largely restricted to substrates with CFGs, typically amides, carboxylic acids, and alcohols, disposed in the correct orientation.

This dissertation follows the style of *Journal of Organic Chemistry*.

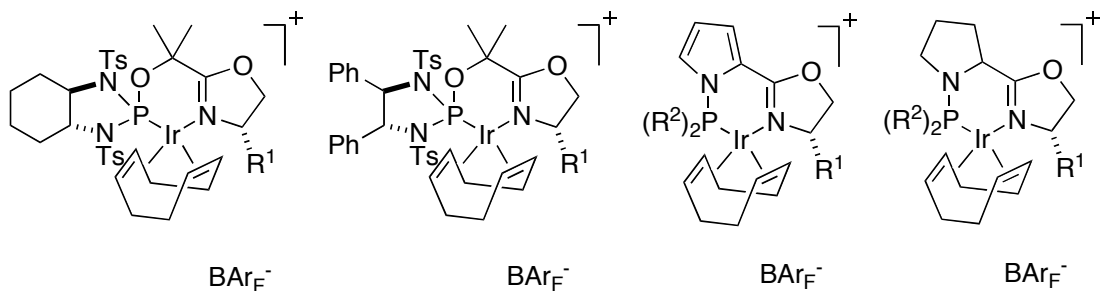
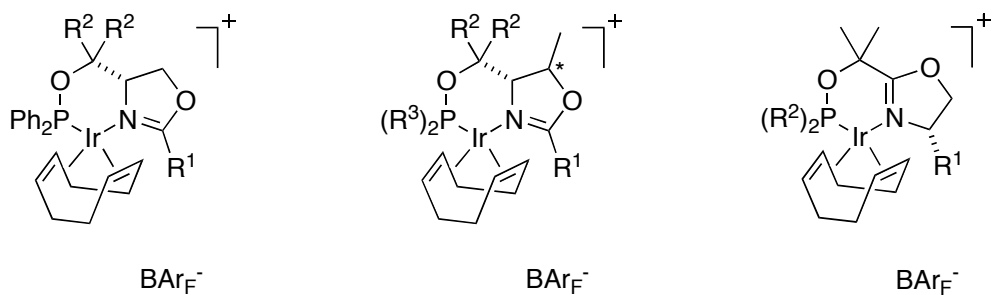
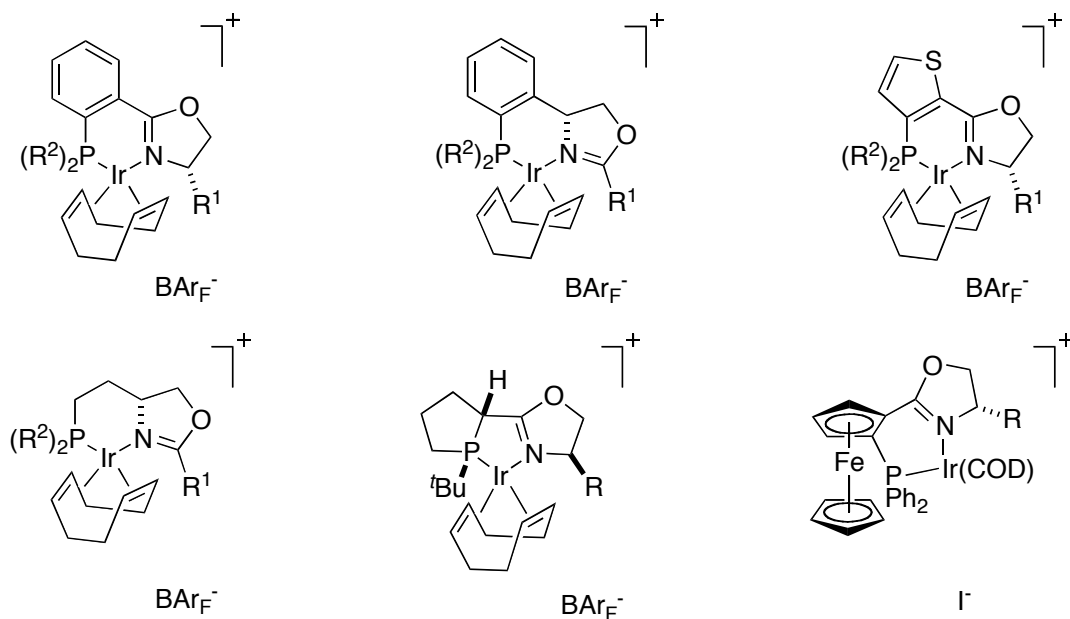
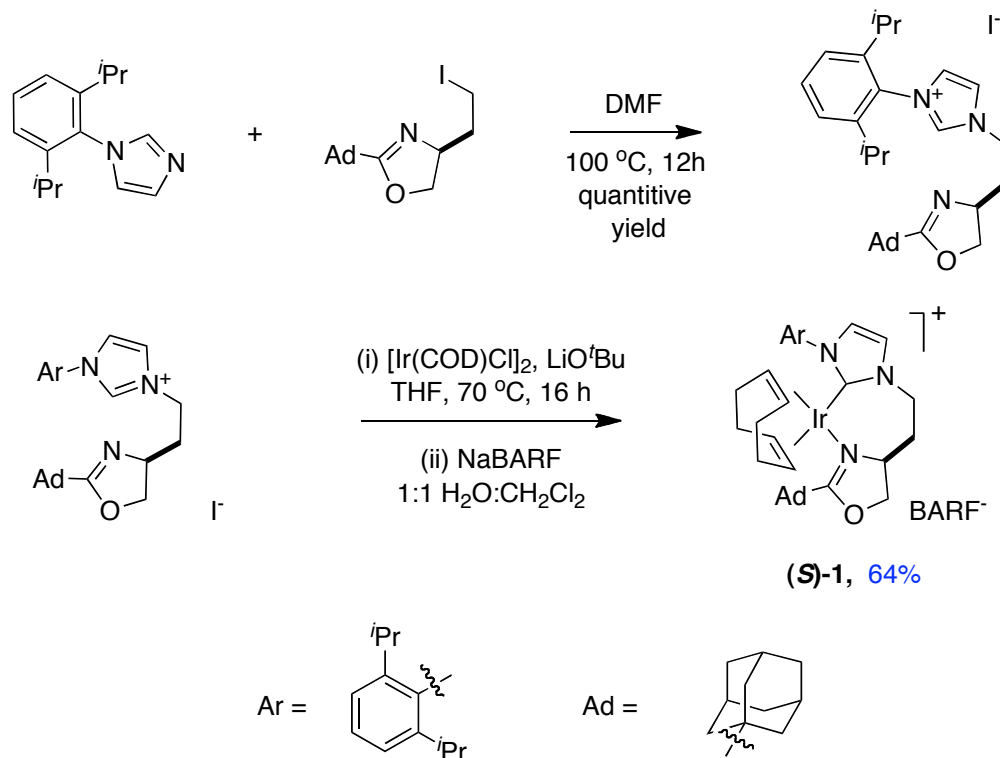


Figure 1.1. Examples of iridium complexes with oxazoline derived *N,P* ligands.

It takes other types of catalyst to hydrogenate alkenes that do *not* have CFGs, and the most useful are the ones based on Crabtree's catalyst, *ie* *N,P*-Ir complexes. In 1998, Pfaltz, *et al*, reported the first chiral analogues of Crabtree's catalyst.¹¹ For a wide range of unfunctionalized olefins, excellent enantioselectivities could be achieved with these complexes. During this research, *tetrakis*[3,5-bis(trifluoromethyl)phenyl]borate (BARF^-) was found to be a much better counterion than hexafluorophosphate (PF_6^-). Iridium complexes with this bulky, apolar, and extremely weakly coordinating anion did not suffer from deactivation, and full conversion could be routinely obtained with catalyst loadings as low as 0.02 mol %.¹² In addition, the BARF salts proved to be much less sensitive to moisture than the corresponding hexafluorophosphates. This success has inspired a lot of research into chiral *N,P*-ligands for enantioselective hydrogenations. The largest and most successful group of chiral analogues of the Crabtree's catalyst are iridium complexes with oxazoline derived *N,P*-ligands¹³⁻²¹ (Figure 1.1).

Scheme 1.1. Synthesis of iridium catalyst bearing NHC-oxazoline ligand.



As *N*-heterocyclic carbenes (NHCs) are frequently regarded as the mimics of phosphines, they are suitable components for the construction of *N,carbene*-analogues of Pfaltz's catalyst. In 2001, our group reported the first highly effective *N,carbene*-Ir catalyst for the asymmetric hydrogenation of trisubstituted unfunctionalized alkenes.^{22,23} The NHC-oxazoline bidentate ligand is derived from an imidazolium salt, which is easily handled, robust, and air-stable. This salt is obtained from an oxazoline electrophile and an imidazole. The catalyst **1** can be made from the salt by reacting with an iridium precursor and exchanging the anion of the complex formed with *tetra*-(3,5-ditrifluoromethylphenyl)borate (BARF⁻).²³ Both the (*R*)-**1** and (*S*)-**1** can be made through the same routes, but starting from enantiomers of dimethyl aspartate, both of which are commercial available (Scheme 1.1). My dissertation research throughout my Ph.D studies has been related to the applications of catalyst **1**.

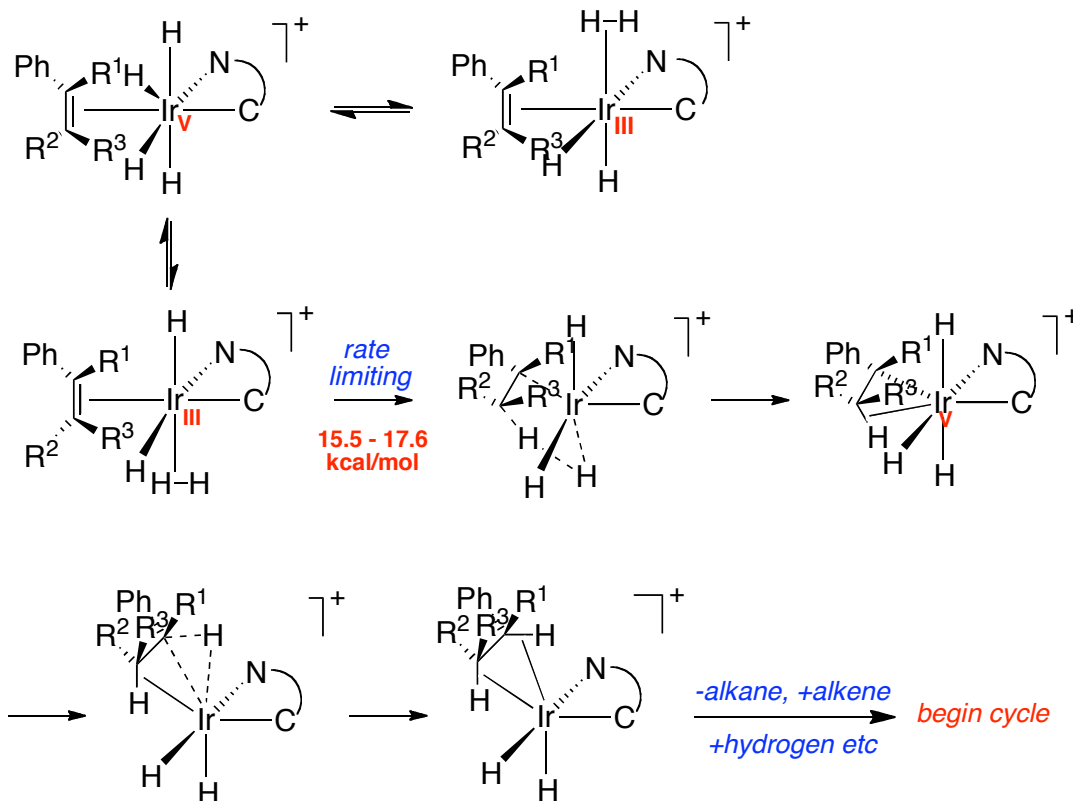


Figure 1.2. Iridium catalyzed hydrogenation pathways via DFT calculations.

Contrary to the case for rhodium catalysts, the mechanism(s) of action of chiral Crabtree's catalyst (or chiral analogs) has not been experimentally proven. Recently though our group^{24,25} and others²⁶ have collected relevant kinetic and spectroscopic data, because of the challenges associated with multiple highly fluxional intermediates in a catalytic cycle that turns over rapidly, a convincing conclusion for the most possible mechanism still can not be made. This is unfortunate because Crabtree's catalyst analogs may evolve to the stage where they are more important than Wilkinson's catalyst derivatives. We^{24,27-29} and others³⁰ used high level DFT calculations to study the hydrogenations by chiral Crabtree catalyst analogs, and reached very similar conclusions. Basically, the metal undergoes not one but two oxidative additions of hydrogen oxidizing the Ir(1+) to a seven-coordinate Ir(5+) tetrahydride. This complex is in a fast equilibrium with two isomers of Ir(3+) dihydrogen dihydrides, which is important because it allows some flexibilities for the following migratory insertion and reductive elimination steps before rate limiting transfer of hydrogen to the coordinated alkene (Figure 1.2). This explains why only Crabtree's catalyst, and not Wilkinson's, hydrogenates tri- and tetra-substituted alkenes at a significant rate: the metal center is more electrophilic (Ir(5+) vs Rh(3+)) and less hindered (the iridium is seven-coordinate and the four hydride ligands are small). Also hydrogenations with these Ir complexes are not particularly sensitive to oxygen, as expected for high oxidation state Ir intermediates. Involvement of Ir(5+) tetrahydride intermediates also explains why the catalytic cycle is so hard to follow spectroscopically because these tetrahydrides are in rapid, dynamic equilibrium with dihydrido-dihydrogen complexes.

1.2 Asymmetric hydrogenations with chiral iridium catalysts

1.2.1 Enantioselective hydrogenations

Pfaltz's success in stereoselectively hydrogenating unfunctionalized olefins inspired many efforts to design other iridium complexes for this purpose. Developments in this field have been the subject of several reviews.³¹⁻³⁵ Actually at one time,

hydrogenation of alkenes with no functional groups (only alkyl substituents) was considered to be a “holy grail” in asymmetric hydrogenations,³⁶ but in 2005 our group reviewed the area and reached a different conclusion.³¹ Research on chiral analogs of Crabtree’s catalyst had produced literally hundreds of *N,P*-ligands, but had applied them to less than *ca* 20 simple alkene substrates (Figure 1.3). Asymmetric hydrogenation products are most useful if they can be used as chiral building blocks, chirons. This requires such chirons have at least one functional group (FG) for modification. Alkenes that have only alkyl substituents give alkanes on hydrogenation, and these are *not* useful chirons.

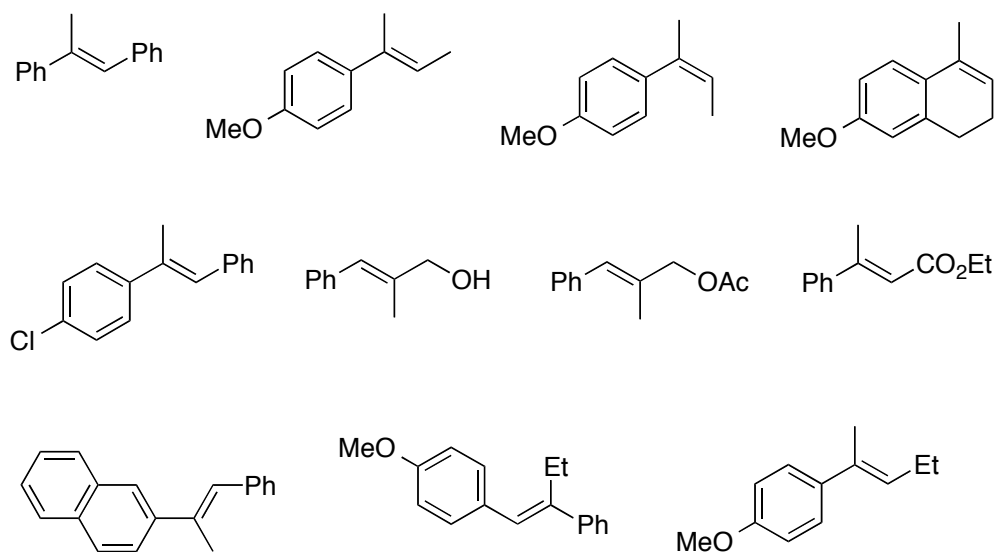


Figure 1.3. Most frequently studied hydrogenation substrates.

There are a huge number of trisubstituted alkenes with FGs that are generally not thought of as coordinating, *ie* not CFGs, so these alkenes are *not* hydrogenated at any significant rate by Wilkinson’s catalyst analogs. However hydrogenations of these substrates could give useful chirons if hydrogenated with high enantioselectivities (*eg* using chiral analogs of Crabtree’s catalyst). This category encompasses a far broader array of substrates than those that have only CFGs, and asymmetric hydrogenations of these alkenes are wide open for development. Indeed, recently iridium catalysts have

been applied to the hydrogenation of olefins with non-coordinating functional groups, including vinyl phosphonates,³⁷⁻⁴⁰ vinyl fluorides,^{41,42} CF₃-substituted olefins,⁴³ vinyl silanes,⁴⁴ enol phosphinate esters,^{45,46} enol ethers,^{13,47} vinyl boronates,⁴⁸ enamines,⁴⁹⁻⁵¹ and even heteroaromatic rings.⁴ Excellent yields and enantioselectivities have been observed in many of these reactions (Figure 1.4).

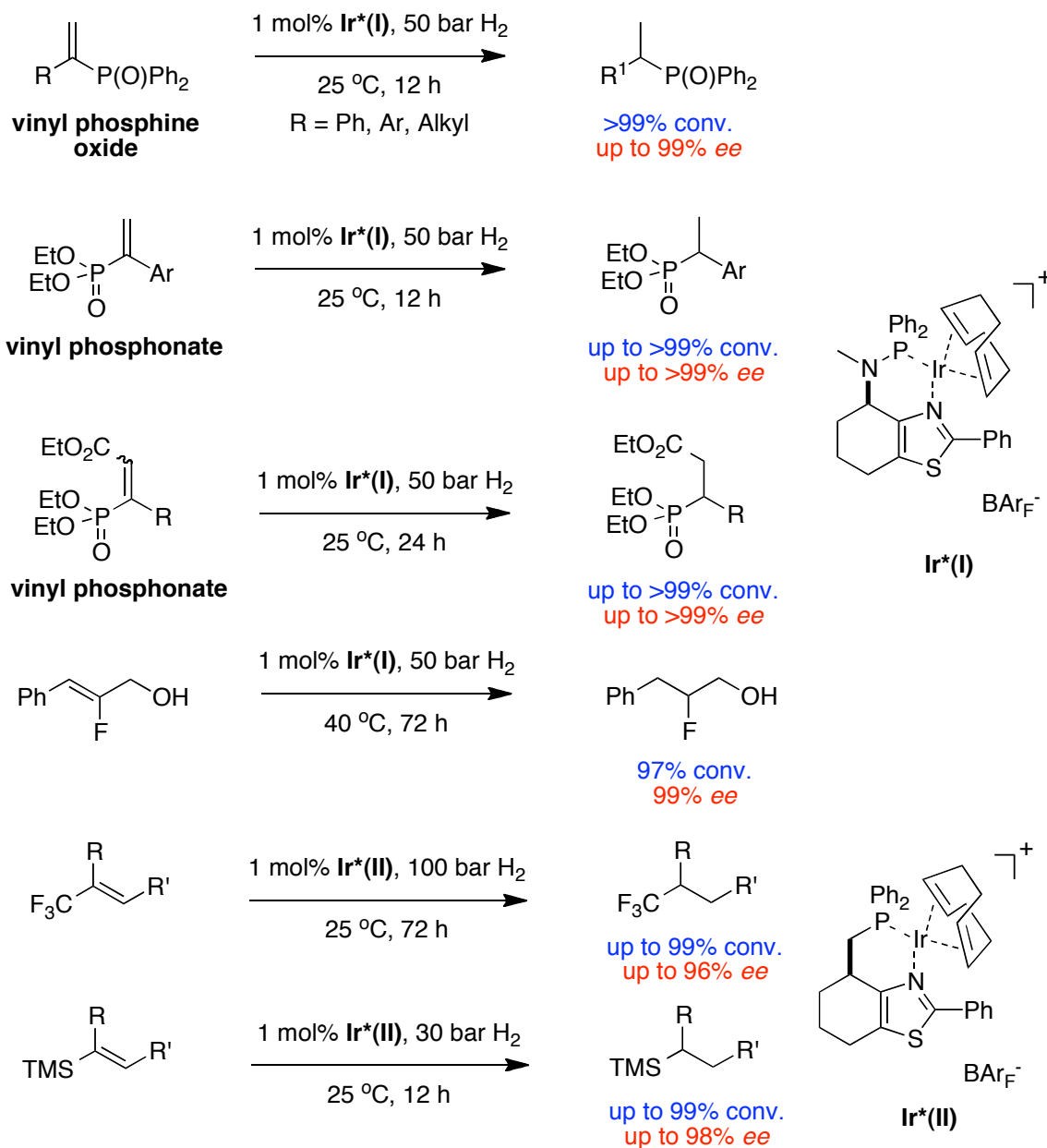


Figure 1.4. Iridium catalyzed enantioselective hydrogenation of alkenes with non-coordinating functional groups.

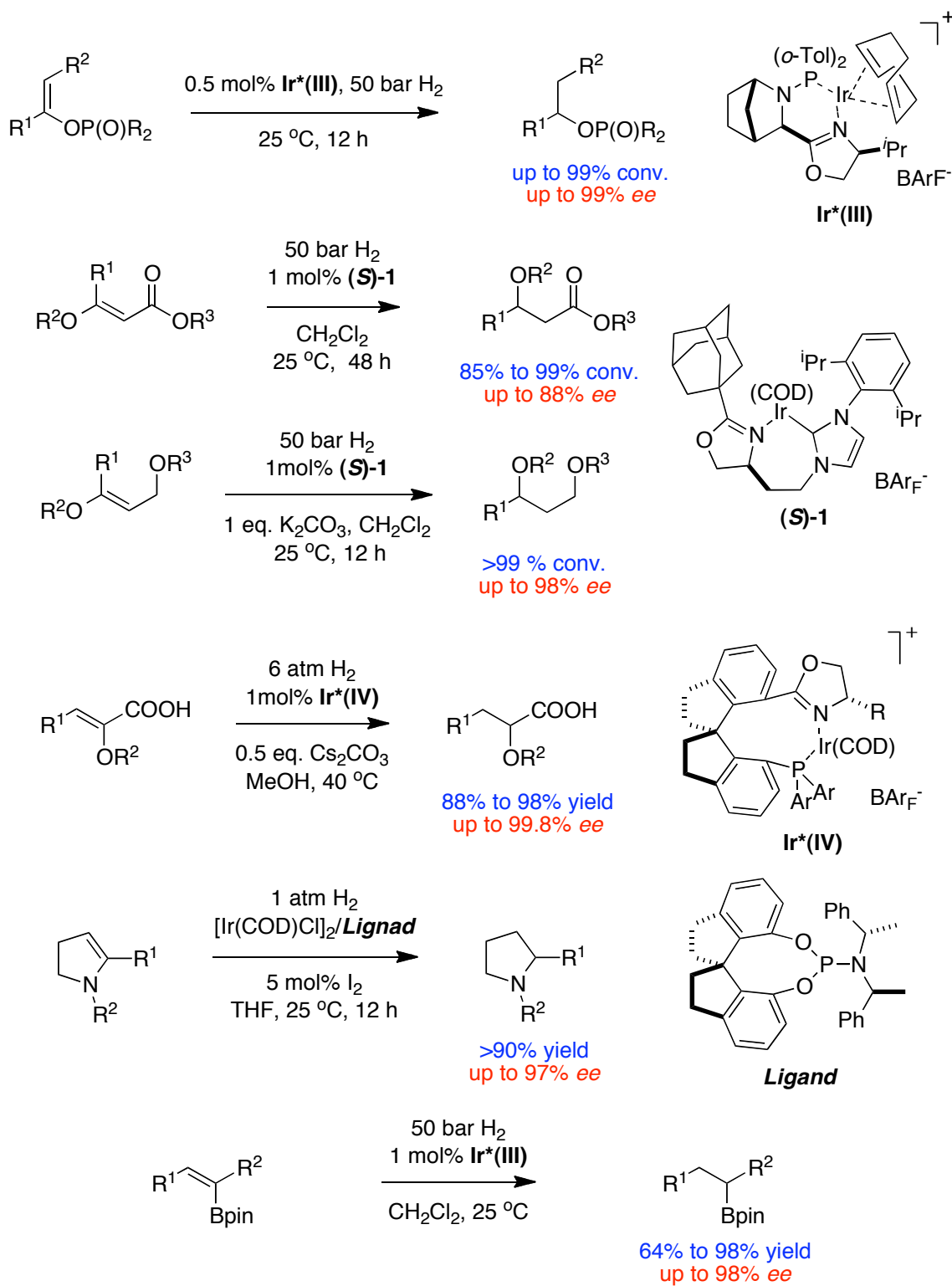


Figure 1.4. continued.

1.2.2 Diastereoselective hydrogenations

In enantioselective hydrogenation, stereochemical control is performed through the selection of one diastereomeric intermediate composed of a prochiral (achiral) substrate and a chiral metal complex. In the hydrogenation of compounds with a stereogenic center, by selecting the catalyst, diastereoselective hydrogenation can induce excellent stereoselectivity via double stereo-differentiation (matched pair).⁵² By linking the steric factor of the stereogenic center of substrates with the chiral inducing ability of properly designed ligands, homogeneous diastereoselective hydrogenation can attain high level of stereoselectivities for optically active compounds with several stereogenic centers.

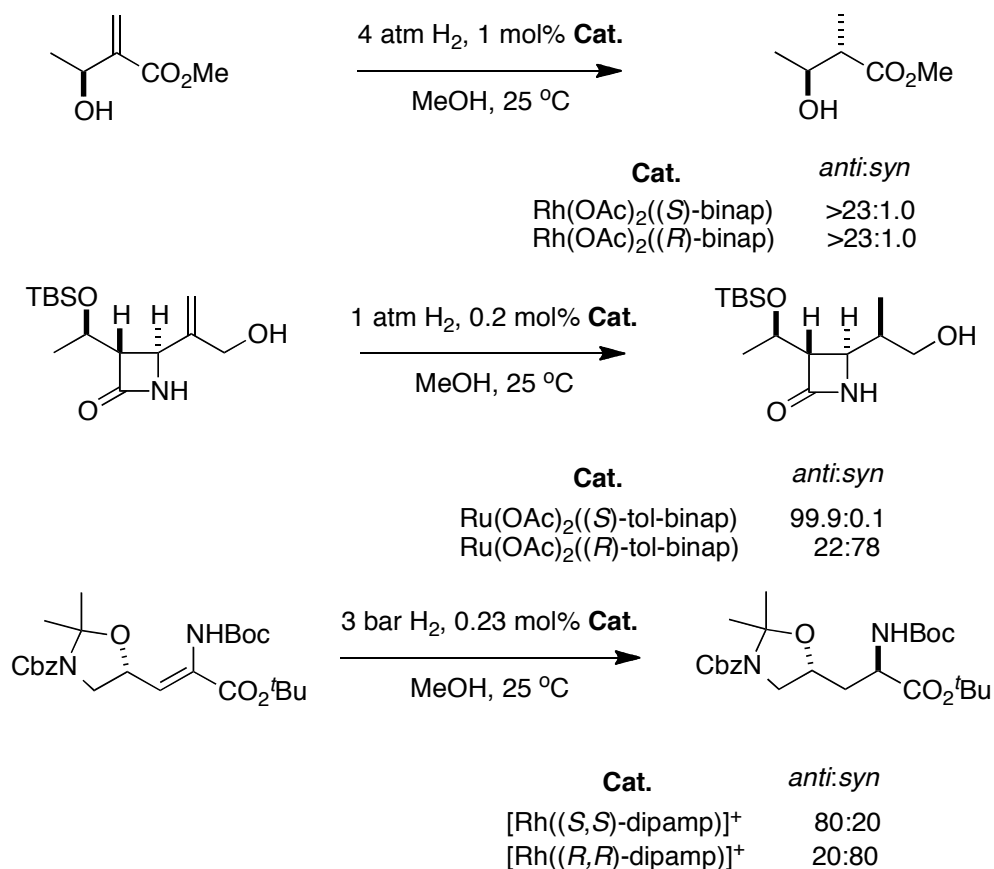


Figure 1.5. Chiral transition-metal catalyst catalyzed diastereoselective hydrogenations of allylic alcohols.

Research into directed hydrogenations for acyclic stereocontrol peaked in the 1980s.⁵³ Much of that work involved 1,1-disubstituted alkenes that are sterically non-

congested and easy to hydrogenate. Those reactions were mostly substrate-controlled, so it was not possible to obtain both diastereoisomers of the hydrogenation product by varying the catalyst chirality alone⁵⁴⁻⁵⁶ (Figure 1.5). Examples involving trisubstituted alkenes are rarer, and tend to feature homoallylic alcohols.⁵⁷ In these cases high diastereoselectivities are possible because simultaneous coordination of the metal to the hydroxyl and alkene gives rigid, chair-like intermediates.⁵⁸ However, those reactions were also mostly substrate controlled (Figure 1.6). Despite recent huge success of chiral iridium catalysts on the asymmetric hydrogenation of olefins with non-coordinating functional groups, few investigations of acyclic stereocontrol have focused on optically active analogs of Crabtree's catalyst. This is a significant gap in the literature because of the well-known matching and mismatch effects.⁵²

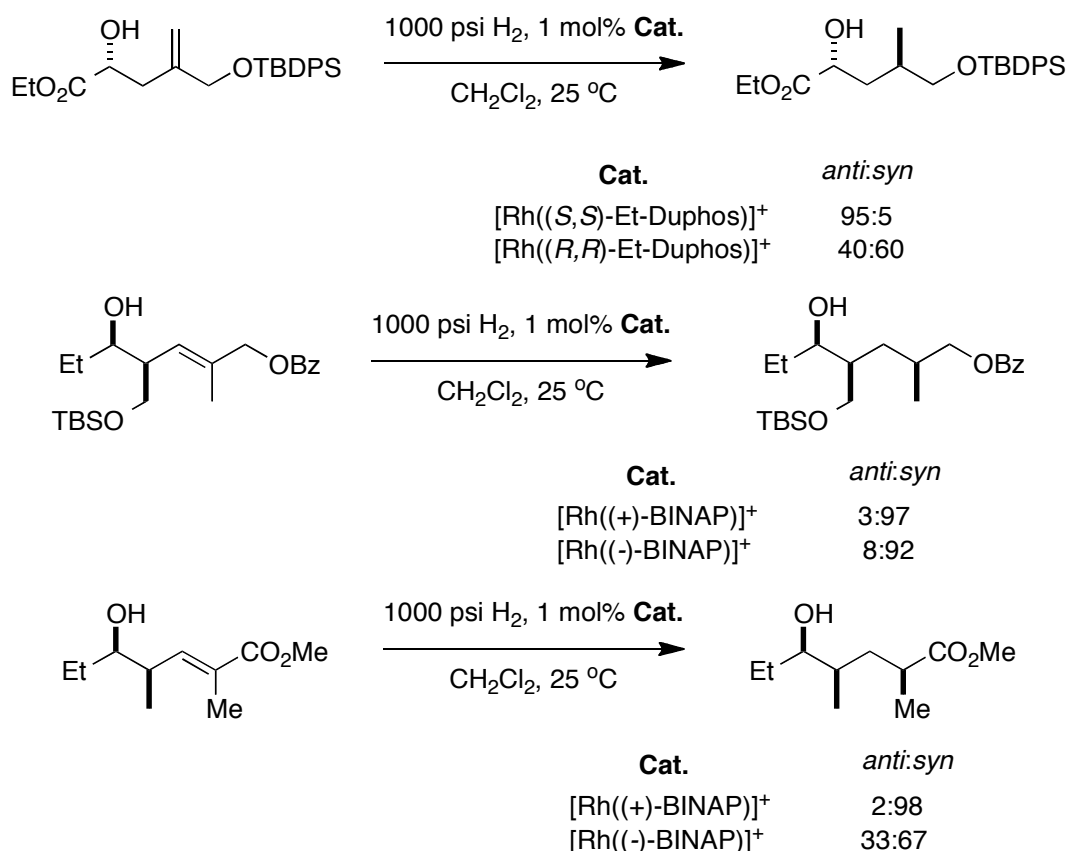
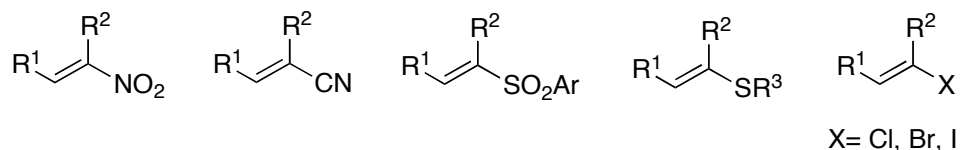


Figure 1.6. Chiral transition-metal catalyst catalyzed diastereoselective hydrogenations of homoallylic alcohols.

1.3 Conclusion

Chiral analogues of Crabtree's catalyst have emerged as a new class of highly efficient catalysts for asymmetric hydrogenation, which are largely complementary to rhodium- and ruthenium-diphosphine catalysts. Many substrates that used to be very difficult to hydrogenate can now be hydrogenated with excellent enantioselectivities. Recently, the iridium catalysts have also been applied to substrates with more exotic non-coordinating functional groups. Many valuable chirons can be obtained with high optical purities. However, even excellent yields and enantioselectivities have been observed in some of the reactions, there remain considerable opportunities to optimize the reaction scope and the hydrogenation stereoselectivities. Specifically, many of the reactions are very substrate dependent and good enantioselectivities can only be achieved for certain alkenes. Also the hydrogenation of some other types of alkenes, like nitro alkenes, cyanide alkenes, etc., have never been reported. These challenging substrates want the development of more powerful chiral iridium catalysts.



One logical “global strategy” to evolve catalytic methodology for organic synthesis would be to first develop highly efficient reactions, then enantioselective transformations involving chiral catalysts, and finally diastereoselective transformations with chiral starting materials and chiral catalysts. Since the seminal work of Crabtree about the iridium catalyzed hydrogenation of unfunctionalized alkenes, the first and second stages of this logical “global strategy” have been successfully reached. However, none of the research on using chiral analogs of Crabtree's catalysts has systematically studied chiral substrates in which the chiral center is close enough to influence the stereochemical outcome. My Ph.D. research is mainly about the highly diastereoselective hydrogenations of chiral alkenes with the *N*,carbene-Ir catalyst **1**.

CHAPTER II

ASYMMETRIC HYDROGENATION APPROACHES TO VALUABLE ACYCLIC 1,3-HYDROXYMETHYL CHIRONS*

2.1 Introduction

Carbon chains bearing 1,3,5...*n* polymethyl groups are ubiquitous in natural products. Recently, effective solutions for a flexible, stereocontrolled synthesis of such arrays have been achieved by many organic research groups.^{59,60} Carbon chains bearing

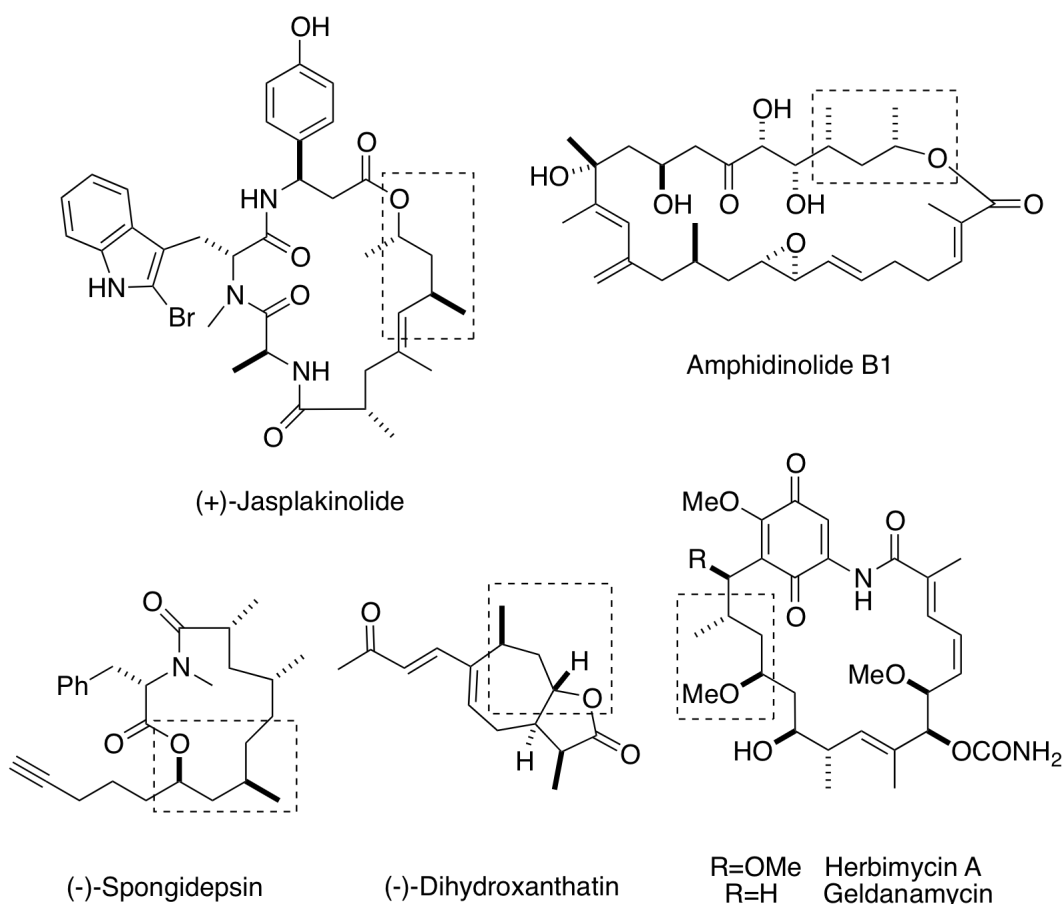
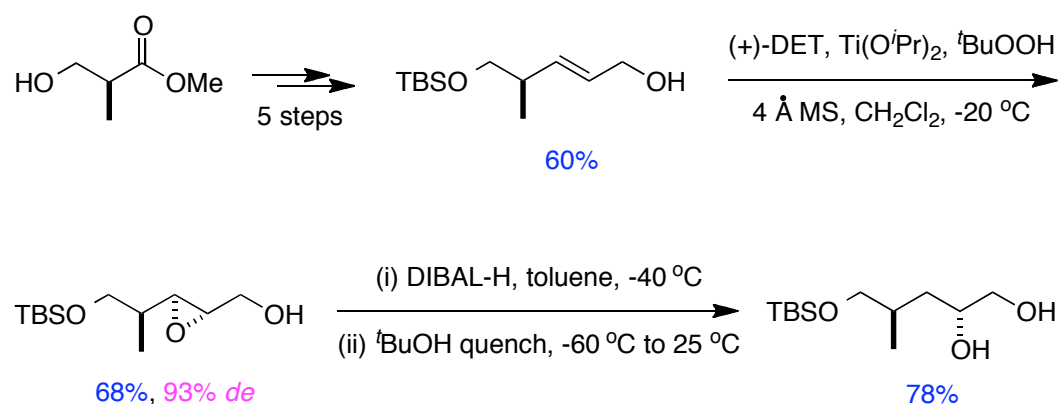


Figure 2.1. 1,3-Hydroxymethyl fragments in polyketide natural products.

*Reprinted in part with permission from “Asymmetric Hydrogenation Approaches to Valuable, Acyclic 1,3-Hydroxymethyl Chirons”, Ye Zhu, Kevin Burgess, *J. Am. Chem. Soc.*, **2008**, *130*, 8894-8895. Copyright 2008 American Chemical Society.

1,3-hydroxymethyl fragments, although less common, are also frequently encountered (Figure 2.1),⁶¹⁻⁶⁶ but synthetic methodologies to obtain these fragments are far from refined; older methods usually feature C-C bond formation reactions like asymmetric zinc addition^{64,67} or allylation⁶⁸ to chiral aldehydes. These methods either have very limited reaction scopes (only Me₂Zn and Et₂Zn can be used) or need use excess of expensive chiral reagents. Recently Furstner *et al* reported a potential solution to this problem.⁶⁹ Starting from commercial available Roche ester, chiral allylic alcohol can be made in five steps. Sharpless asymmetric epoxidation, followed by highly regioselective ring opening gave the 1,3-hydroxymethyl chiron with very good diastereoselectivity (Scheme 2.1). Since both enantiomers of the Roche ester and diethyl tartarate are commercial available, so ideally all the four diastereomers can be obtained via this route.

Scheme 2.1. One recent example for the synthesis of 1,3-hydroxymethyl chiron.



Research into directed hydrogenations for acyclic stereocontrol peaked in the 1980s.⁵³ Much of that work involved 1,1-disubstituted alkenes that are sterically non-congested and easy to hydrogenate. Examples involving *trisubstituted* alkenes are rarer, and tend to feature homoallylic alcohols.⁵⁷ In these cases high diastereoselectivities are possible because simultaneous coordination of the metal to the hydroxyl and alkene gives rigid, chair-like intermediates. However, there are relatively few examples of useful acyclic stereocontrol in hydrogenations of trisubstituted alkenes that are *allylic* alcohols, or where no alcohol at all is present. There is a good reason for this. Most of

the work on directed hydrogenations has featured rhodium and iridium catalysts of the type MP_2 where P_2 is a chelating diphosphine ligand, and these do not hydrogenate trisubstituted alkenes at a significant rate if a directing group is not present. This is not so, however, for Crabtree's catalyst⁷⁰⁻⁷³ and analogs of the Ir- N,P type ($N,P = sp^2-N$ ligand and phosphine); they can hydrogenate trisubstituted and even tetrasubstituted alkenes where there are no apparent directing groups.³¹ Few investigations of acyclic stereocontrol, however, have focused on Crabtree's catalyst,^{58,74} and in those the stereoselectivities obtained were poor. Even fewer studies on acyclic stereocontrol have featured optically active analogs of this catalyst; indeed, the first of these complexes was not reported until 1998.¹¹ This is a significant gap in the literature because it is well known that chiral catalysts can constructively couple with substrate biases (matching effects).⁵²

Nearly all the substrates studied before 2005 in hydrogenations mediated by chiral analogs of Crabtree's catalyst give relatively simple, uninteresting products.³¹ To access more sophisticated chirons, our group launched a program to study hydrogenations of dienes and polyenes,^{24,25,75} and Pfaltz *et al* recently reported reduction of a 1,5,9-triene to give (*R,R,R*)-tocopherol.⁷⁶ The latter work stands out as a synthetically very useful application of chiral Crabtree's catalyst analogs. However, although it is formally a diastereoselective synthesis, the pre-existing chiral center in the substrate was too far away from the nearest alkene to affect the face selectivity. In 2007, our group reported a systematic study of the asymmetric hydrogenations of chiral substrates in which the chiral center is close enough to influence the stereochemical outcome. This study resulted a highly practical methodology for the 1,3,5...*n* polymethyl fragment synthesis⁷⁷ (Figure 2.2). This route is competitive with the other state-of-art methods, in terms of catalyst loading, stereoselectivities, and atom economy. It proved that the chiral analogues of Crabtree's catalyst, unlike diphosphine systems for the same substrates, could exert strong influences for the diastereoselectivities.^{28,77,78} In other words, catalyst control usually dominated in these hydrogenation reactions.

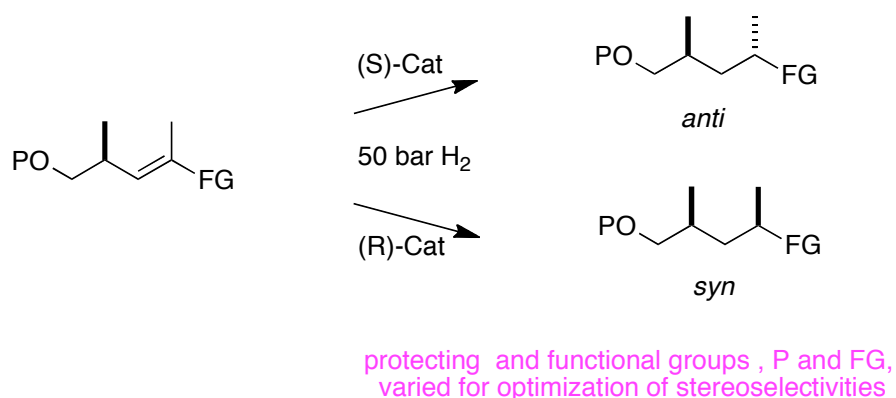


Figure 2.2. Asymmetric hydrogenation routes to 1,3-dimethyl chirons.

Inspired by the above discoveries, an interesting idea rose. We thought that changing the allylic methyl substituent to an alcohol substituent would provide another very interesting type of substrates for the hydrogenation. The catalyst might also work well for the hydrogenations of this new type of alkenes. All the substrates featured in the last project were derived from Roche's ester. However, several other readily available natural starting materials could be used to generate related alkenes in a similar way (Figure 2.3). In this chapter, the studies about the asymmetric hydrogenations mediated by complex **1** to afford the “internal” and “terminal” chirons **A** and **B** found in many natural products and useful derivatives will be described.⁷⁹

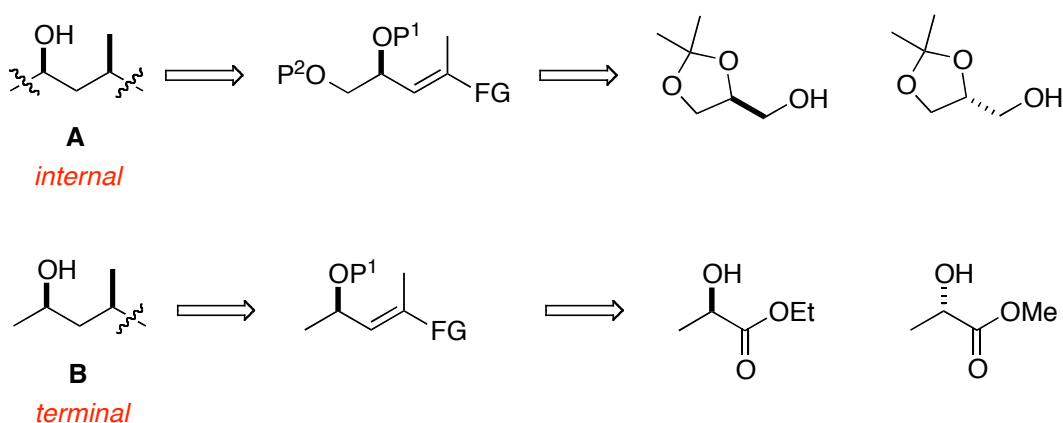


Figure 2.3. Asymmetric hydrogenation routes to 1,3-hydroxymethyl chirons.

2.2 Results and discussions

2.2.1 Syntheses of the internal fragments

Syntheses of substrates to prepare the internal fragments **A** began with glycidol acetonide (conveniently available as either enantiomer).⁸⁰ Hence alkene **3-8** were prepared straightforward (Scheme 2.2). Only alkene **5, 6, 8** were hydrogenated and the hydrogenation data were shown in Table 2.1. The alkene **5** did not give high selectivities with both enantiomers of the catalyst, but excellent data were obtained for **6** and **8**.

Scheme 2.2. Routes to alkene substrates for syntheses of internal chiron **A**.

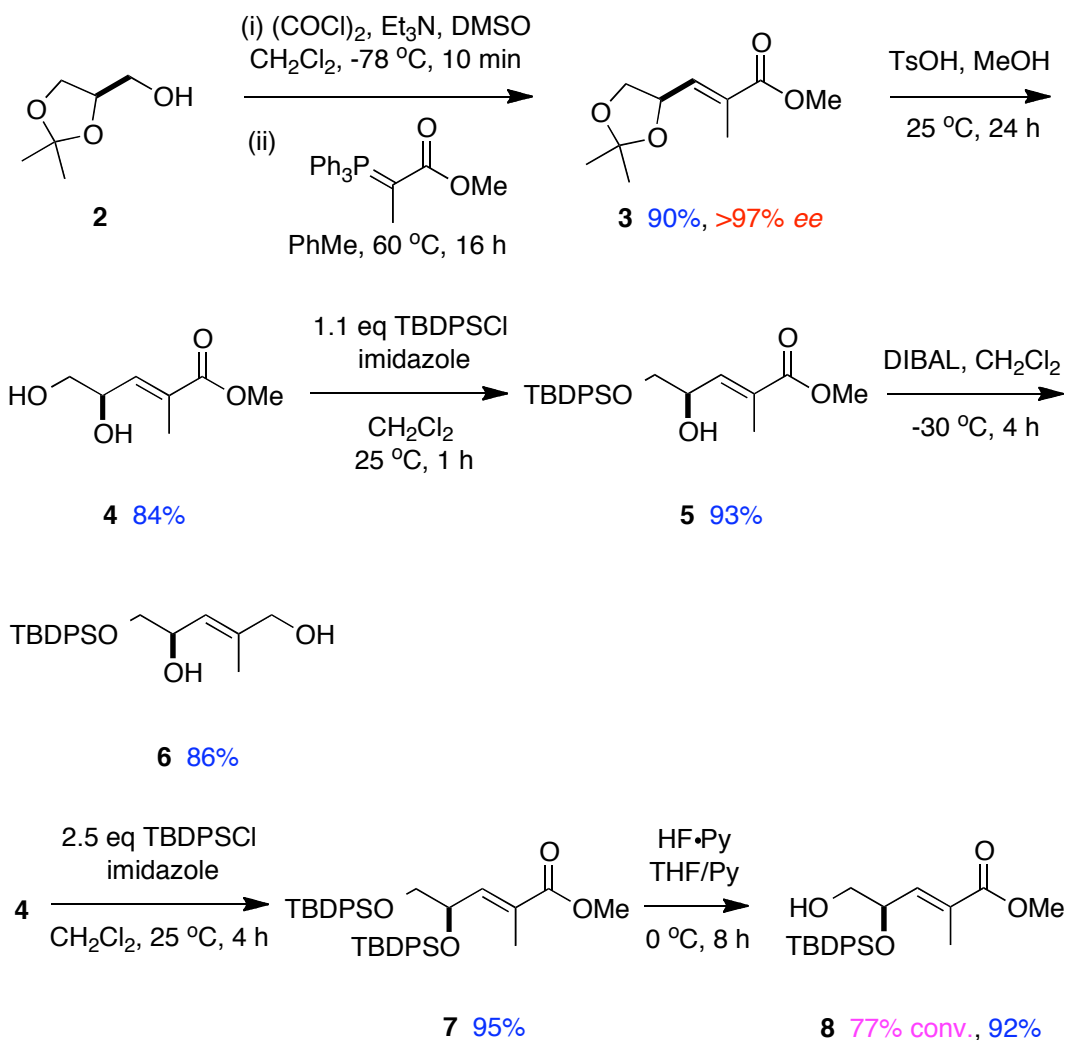
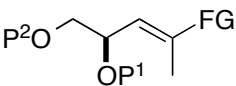
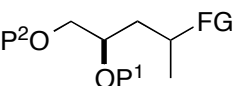


Table 2.1. Hydrogenation of internal hydrogenation substrates.

<div style="display: flex; align-items: center; justify-content: center;"> <div style="text-align: center;">  </div> <div style="text-align: center; margin: 0 20px;"> $\xrightarrow[\text{CH}_2\text{Cl}_2, 25\text{ }^\circ\text{C}, 4\text{ h}]{50\text{ atm H}_2, 1\text{ mol \% Ir}^*}$ </div> <div style="text-align: center;">  </div> </div> <p style="text-align: center; margin-top: 5px;">>99% conv.</p> <p style="text-align: center; margin-top: 5px;"><i>syn or anti</i></p>						
Entry	Substrate	P ¹	P ²	FG	Ir* (cat)	<i>syn:anti</i> ^{a,b}
1	5	H	TBDPS	CO ₂ Me	(S)-1	1.0:3.3
2	5	H	TBDPS	CO ₂ Me	(R)-1	1.0:2.3
3	6	H	TBDPS	CH ₂ OH	(S)-1	14:1.0
4	6	H	TBDPS	CH ₂ OH	(R)-1	1.0:24
5	8	TBDPS	H	CO ₂ Me	(S)-1	17:1.0
6	8	TBDPS	H	CO ₂ Me	(R)-1	19:1.0

^a absolute chemistry was determined by comparison of the optical rotation value with reported one. ^b the diastereomer ratio were measured by GC.

Formation of the *syn* product **9** is an excellent reaction because this lactone is crystalline and it can be recrystallized from the crude material without column chromatography (Figure 2.4.a). In both reactions, the diastereoselectivity is extremely high. A chair-like intermediate can be used to rationalize preferential formation of the product **9**, so this is a typical directed hydrogenation of a homoallylic alcohol via *substrate* control (Figure 2.4.c). Formation of **10**, however, is *catalyst* controlled. In that case there is a substrate vector based on conformers preferred by 1,3-allylic strain considerations, and possibly some directing effect from the allylic alcohols; however, these two factors modulate, but do not overcome, the catalyst vector (Figure 2.4.b and 2.4.d).

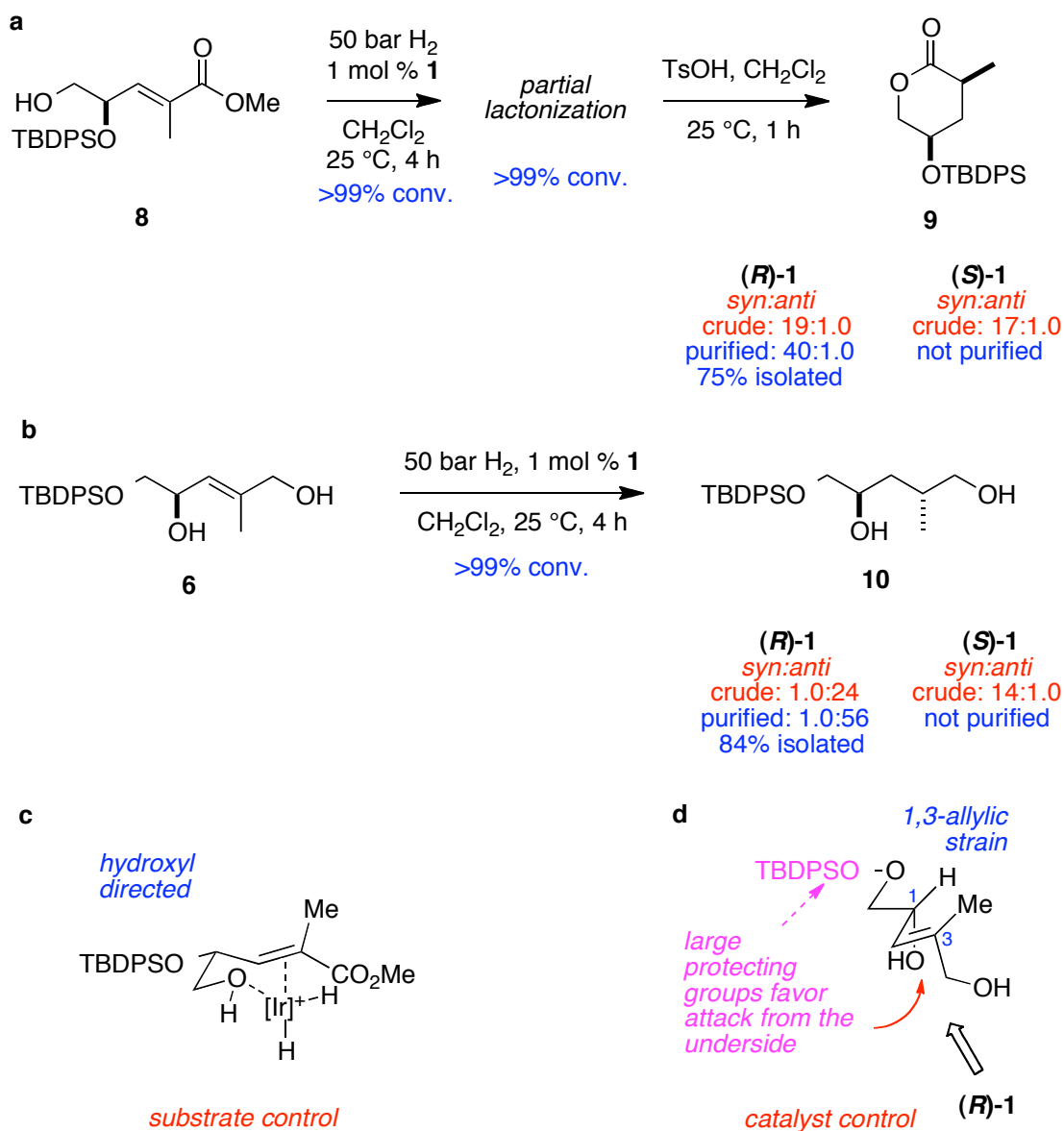


Figure 2.4. Preparation of: **a** a *syn*-type **A** chiron; and, **b** an *anti*-type **A** chiron. All ratios quoted are from GC. **c** Directed hydrogenation model gives substrate control; and, **d** catalyst control dominates where the substrate conformation is only held by 1,3-allylic strain.

2.2.2 Syntheses of the terminal fragments

A similar approach was used to obtain optically pure *syn* and *anti*-isomers corresponding to the terminal fragment **B**, except that lactic acid was the starting material. Starting from commercial available (*S*)-lactic acid, enantiomeric pure **12** can

be made via silyl protection, reduction, and Wittig olefination sequence. Starting from this key intermediate, seven relevant substrates were prepared with high yields (Scheme 2.3). The hydrogenation data were listed in Table 2.2. Hydrogenations of **12**, **13**, **15**, **16** did not provide good diastereoselectivities, but excellent data were obtained for **14**, **17** and **18**.

Scheme 2.3. Routes to alkene substrates for the syntheses of terminal chiron **B**.

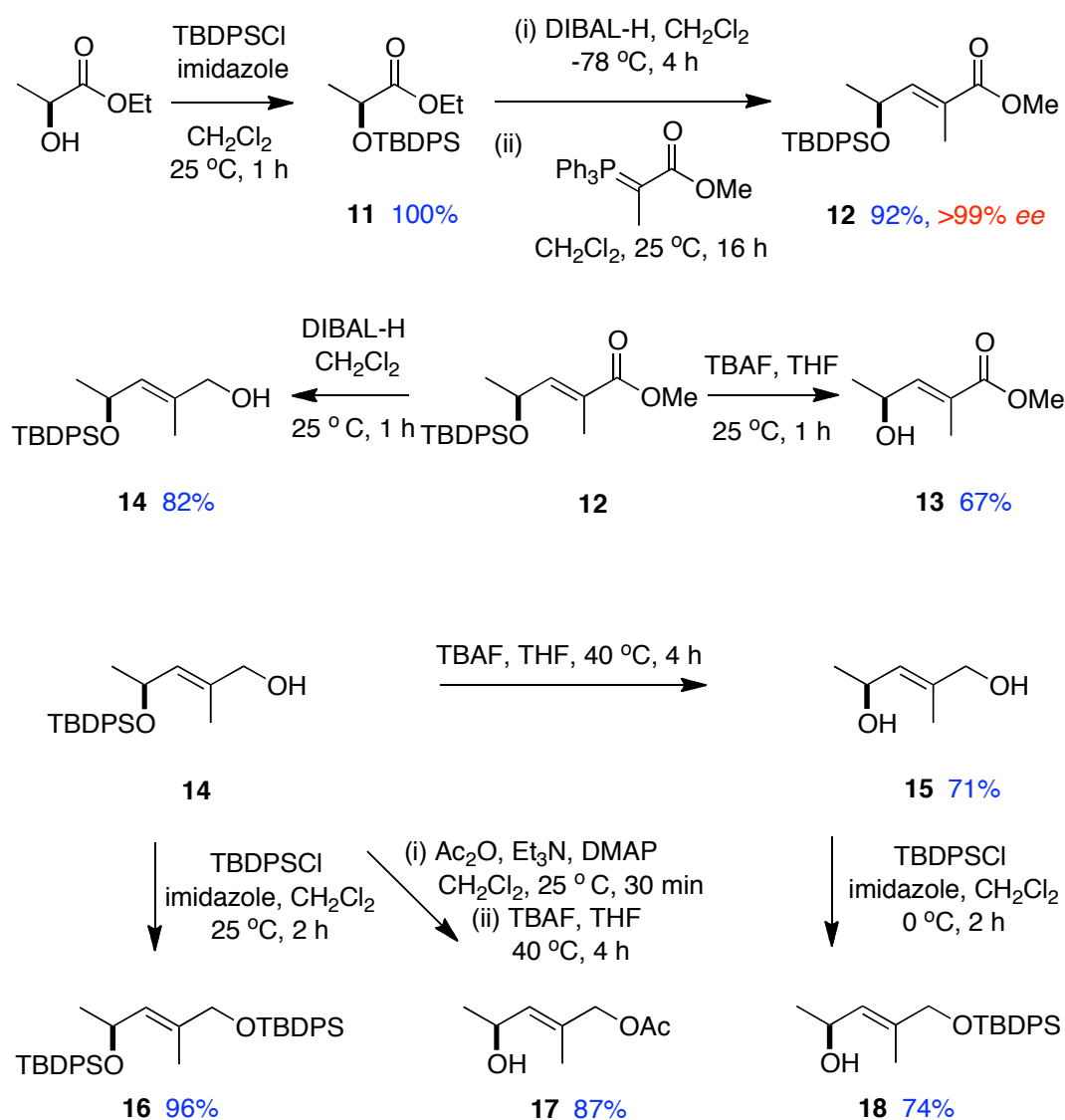


Table 2.2. Hydrogenation of terminal hydrogenation substrates.

Entry	Substrate	P ¹	FG	Ir* (cat)	syn:anti ^{a,b}
1	12	TBDPS	CO ₂ Me	(<i>S</i>)- 1	3.0:1.0
				(<i>R</i>)- 1	2.4:1.0
2	13	H	CO ₂ Me	(<i>S</i>)- 1	1.0:12
				(<i>R</i>)- 1	1.0:2.0
3	14	TBDPS	CH ₂ OH	(<i>S</i>)- 1	38:1.0
				(<i>R</i>)- 1	1.0:1.1
4	15	H	CH ₂ OH	(<i>S</i>)- 1	3.2:1.0
				(<i>R</i>)- 1	1.0:8.2
5	16^c	TBDPS	CH ₂ OTBDPS	(<i>S</i>)- 1	7.7:1.0
				(<i>R</i>)- 1	8.5:1.0
6	17	H	CH ₂ OAc	(<i>S</i>)- 1	1.0:8.6
				(<i>R</i>)- 1	1.0:57
7	18	H	CH ₂ OTBDPS	(<i>S</i>)- 1	1.0:7.3
				(<i>R</i>)- 1	1.0:55

^a absolute chemistry was determined by comparison with the true sample. ^b the diastereomer ratio were measured by GC. ^c after 24h only ~30% conv. (seeing from ¹H NMR).

Catalyst control dominated for substrate **14** and the optimal stereoselectivity was obtained when the 1,3-allylic strain vector from the substrate matched with the preferred approach of the catalyst (Figure 2.5.c). Hydrogenations of **17** and **18** were substrate controlled. In these two examples the alkene is quite hindered. The simplest explanation for the observed selectivity is in terms of directed attack resulting from

coordination to the allylic alcohol. This could occur via oxygen coordinating with iridium, or via hydrogen bonding from an iridium hydride to the allylic alcohol oxygen (Figure 2.5.d).^{81,82} The latter is possible since recent observations from our group indicate the iridium complex is slightly acidic.^{27,47}

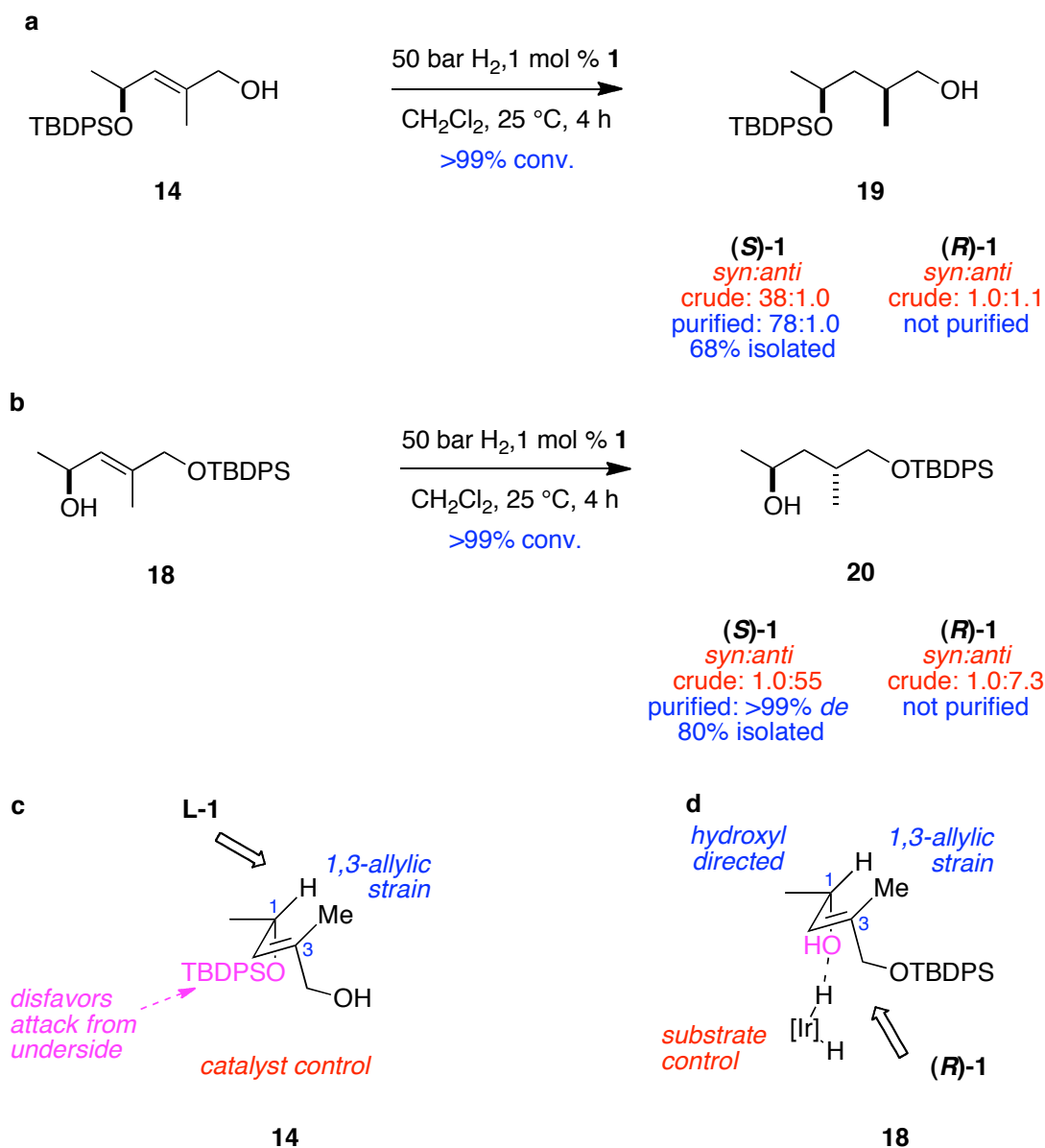
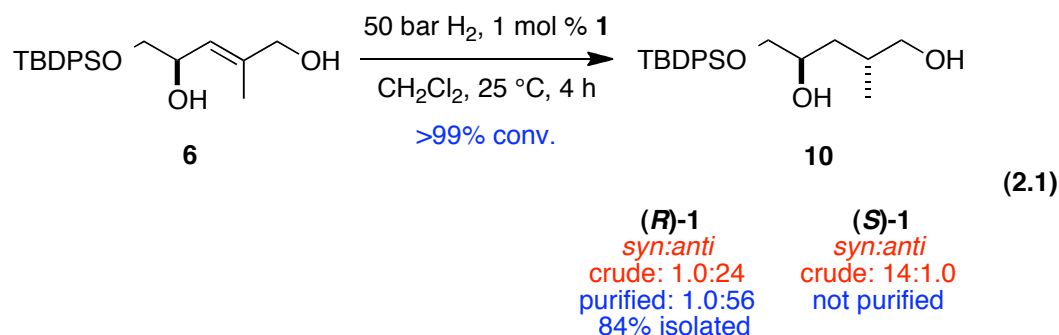


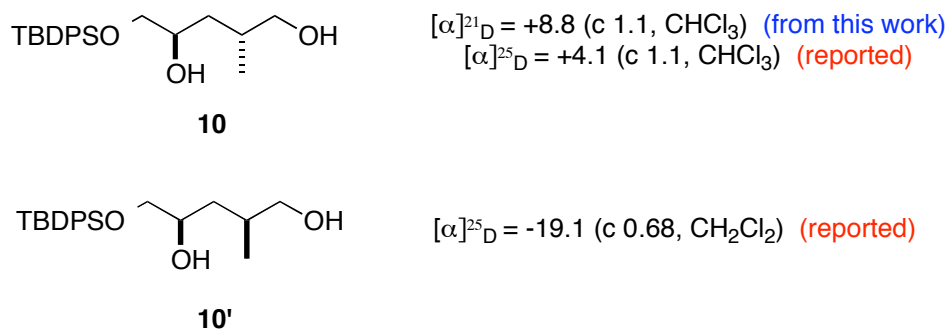
Figure 2.5. Preparation of type **B** chirons: **a** a *syn*-form; and, **b** *anti*-form. All ratios quoted are from GC. **c** Catalyst control dominates where the substrate conformation is only held by 1,3-allylic strain; and, **d** substrate control prevails for substrate **18**.

2.2.3 Relative and absolute configuration determination

2.2.3.1 For the internal chiron A



The alkene **6** was made from enantiomer enriched (*R*)-(-)-glycerol acetone (98% *ee*). So the absolute stereochemistry was determined by the chirality from the starting material. Hydrogenation of **6** with (*R*)-**1** provided the *anti*-isomer of chiron **A** with high diastereoselectivity (*syn:anti*, *dr* 1.0:24) (reaction 2.1). The product **10** was a known compound with reported optical rotation value.⁸³ The optical rotation value for compound **10** obtained from this hydrogenation work was quite close to the reported one. On the other hand, compound **10'**, the *syn* diastereoisomer of **10**, was also a known compound with reported ¹³C NMR and optical rotation value.⁸⁴ Both the ¹³C NMR and optical rotation value of **10'** are significantly different from those data obtained from **10**.



Alkene **8** was hydrogenated with Pd/C to afford a mixture of two diastereoisomers. The crude products were reduced by DIBAL-H and the silyl-protecting group was removed by TBAF. The crude triols were further converted to the corresponding triacetate, which was directly used for gas chromatography (reaction 2.2).

The GC gave a pair of well-separated peaks corresponding to the *syn* and *anti* diastereoisomers (Figure 2.6).

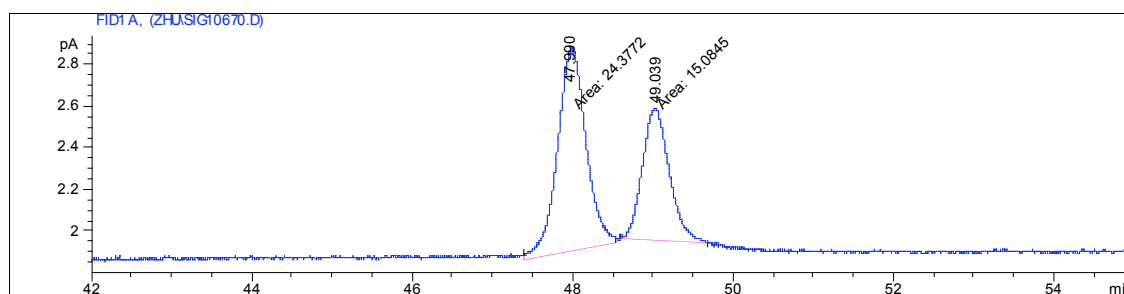
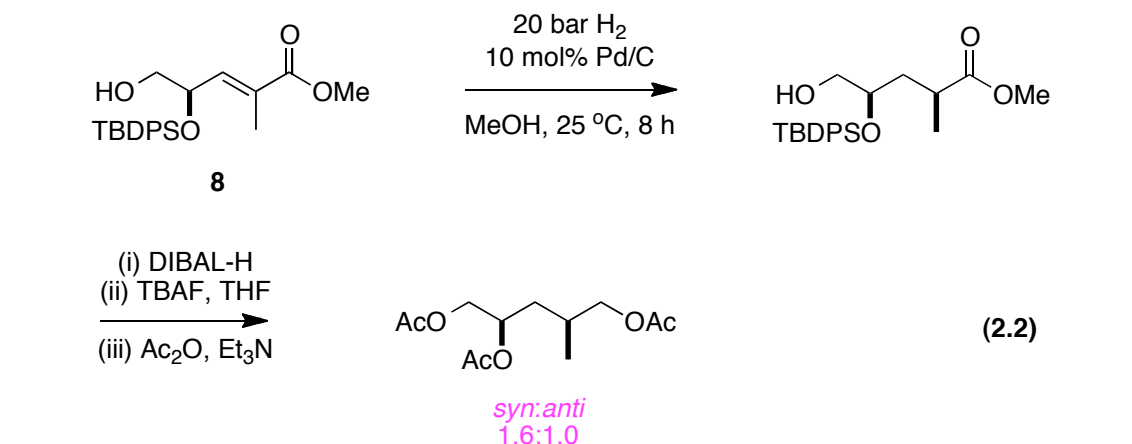


Figure 2.6. GC separation of modified hydrogenation products from Pd/C catalyzed hydrogenation of **8**.

Alkene **6** was hydrogenated efficiently with either (*S*)-**1** or (*R*)-**1**. The hydrogenation product was modified similarly as above. The crude triacetate was also checked by the gas chromatography under the same condition to determine the diastereoisomer ratio. As we already mentioned above, the hydrogenation of alkene **6** with (*R*)-**1** would provide the *anti*-isomer as the major product, so based on the gas chromatography the diastereoisomer ratio was 24:1.0 in favor of the *anti*-isomer. Meanwhile it was clear that the (*S*)-**1** provided the *syn*-isomer for the hydrogenation with a diastereoisomer ratio 14:1.0 (Figure 2.7 and 2.8).

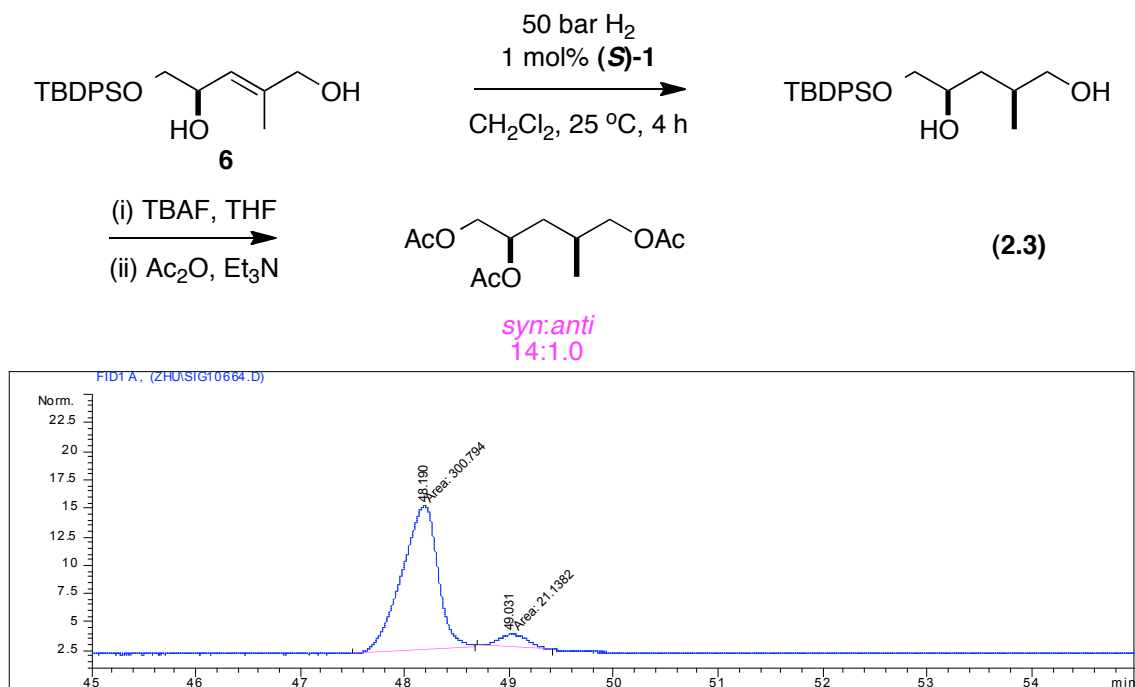


Figure 2.7. GC separation of modified hydrogenation products from **(S)**-1 catalyzed hydrogenation of **6**.

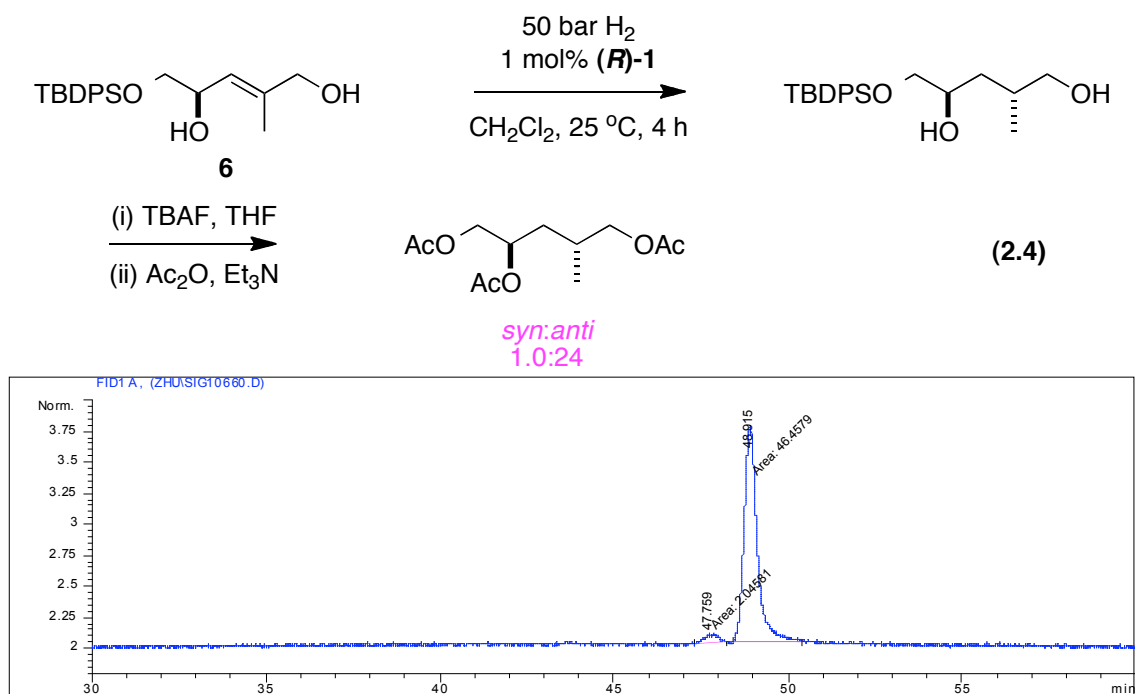
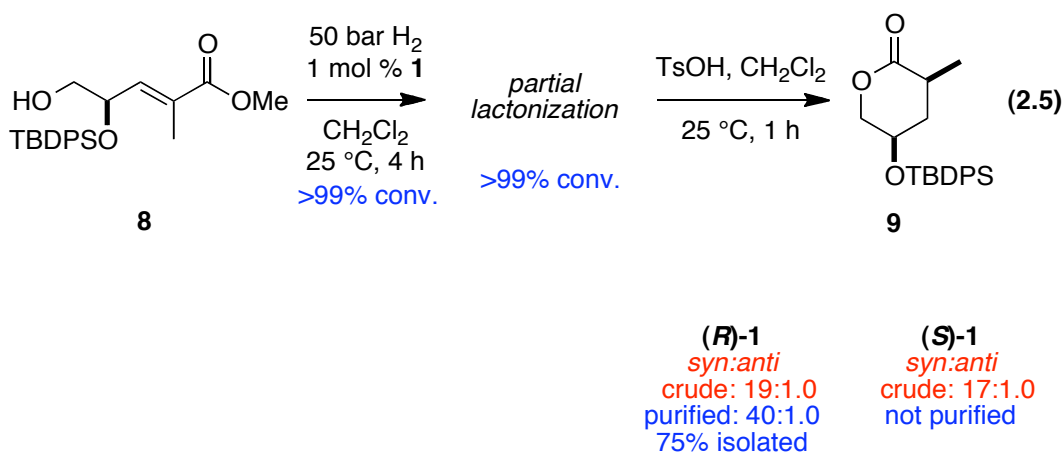


Figure 2.8. GC separation of modified hydrogenation products from **(R)**-1 catalyzed hydrogenation of **6**.



Based on the ^1H NMR, hydrogenation of alkene **8** with (*S*)-**1** and (*R*)-**1** favored the same diastereomer of the hydrogenation product (reaction 2.5). The relative stereochemistry of the product and the diastereoisomer ratio were determined in the following way. First the alkene **8** was hydrogenated using either (*S*)-**1** or (*R*)-**1** to give a mixture of two diastereomers. These were reduced to the diol (DIBAL), the silyl protecting group was removed (TBAF), and the resulting triol was converted to triacetate. The two diastereomers were then separated via GC (same condition as above). The *anti*-isomer of **9**, *ie* compound **10**, is a known compound so the GC peak corresponding to the *syn*-isomer was the other peak. From the GC, it is clear that both (*S*)-**1** and (*R*)-**1** provided the *syn*-isomer of the hydrogenation product. For the (*S*)-**1** the diastereoisomer ratio was 17:1.0 (Figure 2.9); for the (*R*)-**1** the diastereoisomer ratio was 19:1.0 (Figure 2.10).

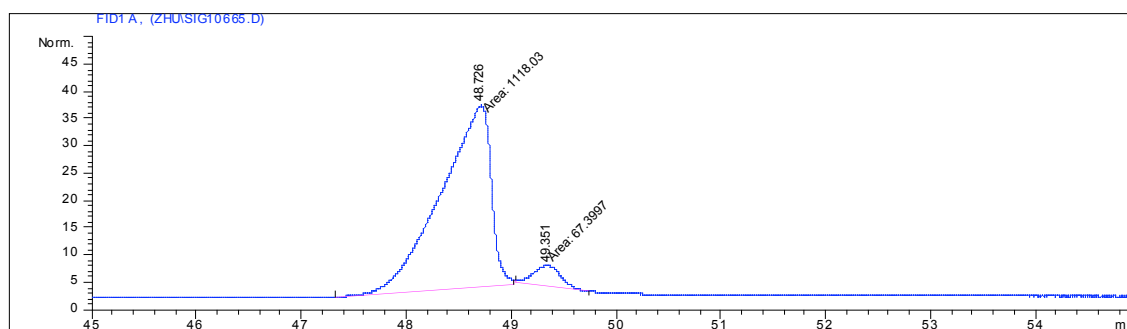
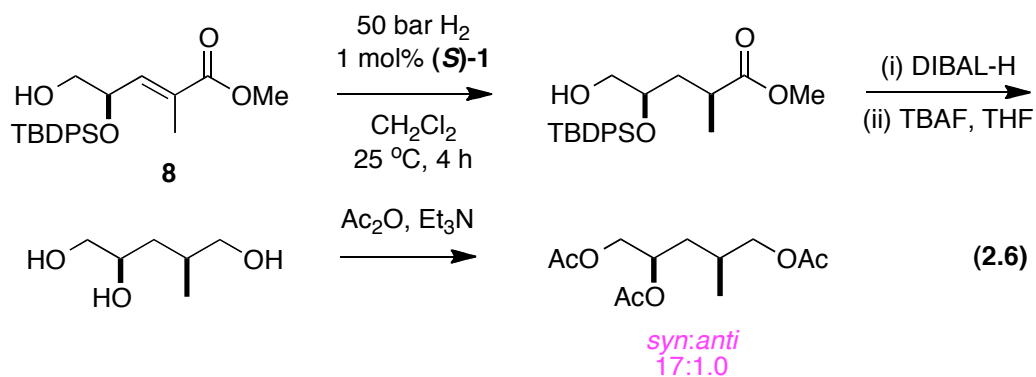


Figure 2.9. GC separation of modified hydrogenation products from (*S*)-**1** catalyzed hydrogenation of **8**.

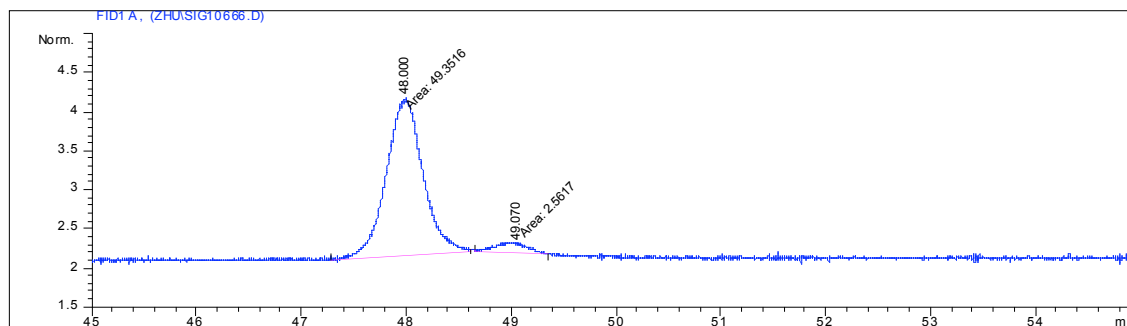
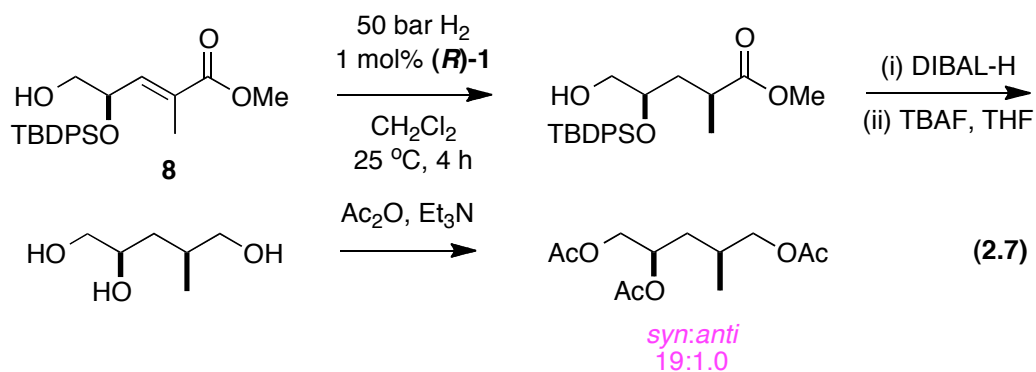


Figure 2.10. GC separation of modified hydrogenation products from (*R*)-**1** catalyzed hydrogenation of **8**.

2.2.3.2 For the terminal chiron B

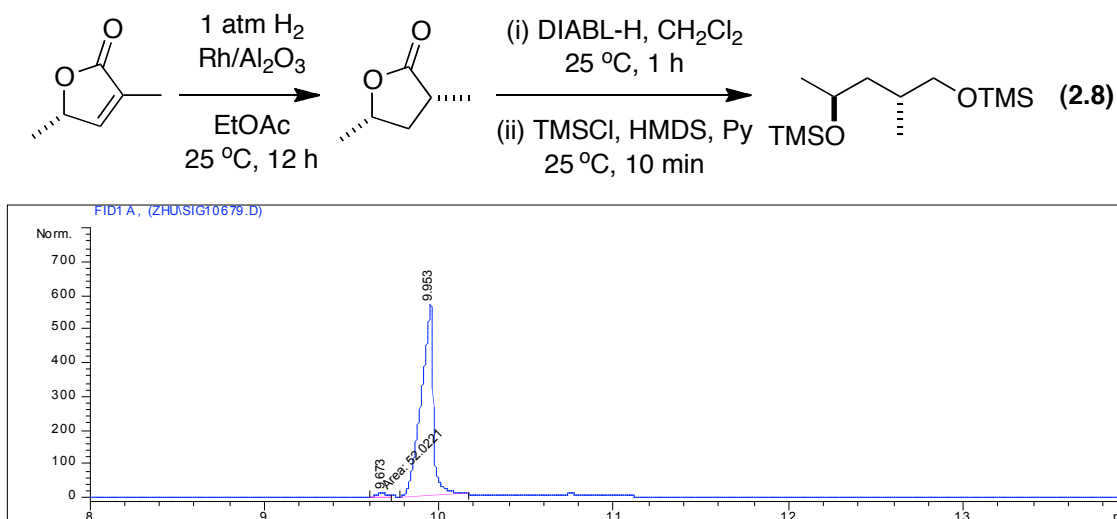


Figure 2.11. GC separation of modified hydrogenation products from $\text{Rh/Al}_2\text{O}_3$ catalyzed hydrogenation of chiral lactone.

The authentic *anti*-isomer of chiron **B** was made via reported literature procedures (reaction 2.8).⁶² The *syn*-dimethyl lactone was reduced to diol (DIBAL), and the resulting diol was converted to the trimethylsilyl ether. The two diastereomers were then separated via GC and the major peak corresponded to the *anti*-isomer (Figure 2.11). The derivative of product **19** gave the different major peak as the authentic compound, which corresponds to the *syn*-isomer (Figure 2.12). The derivative of product **20** gave the same major peak as the authentic compound, which corresponds to the *anti*-isomer (Figure 2.13).

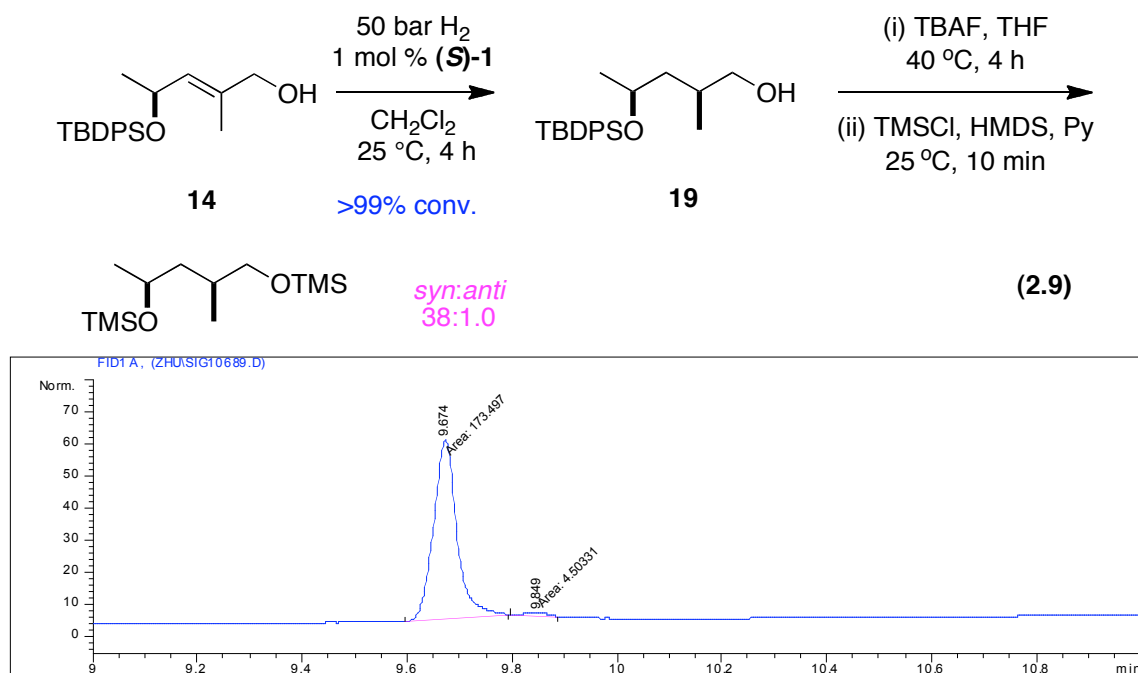


Figure 2.12. GC separation of modified hydrogenation products from **(S)**-**1** catalyzed hydrogenation of **14**.

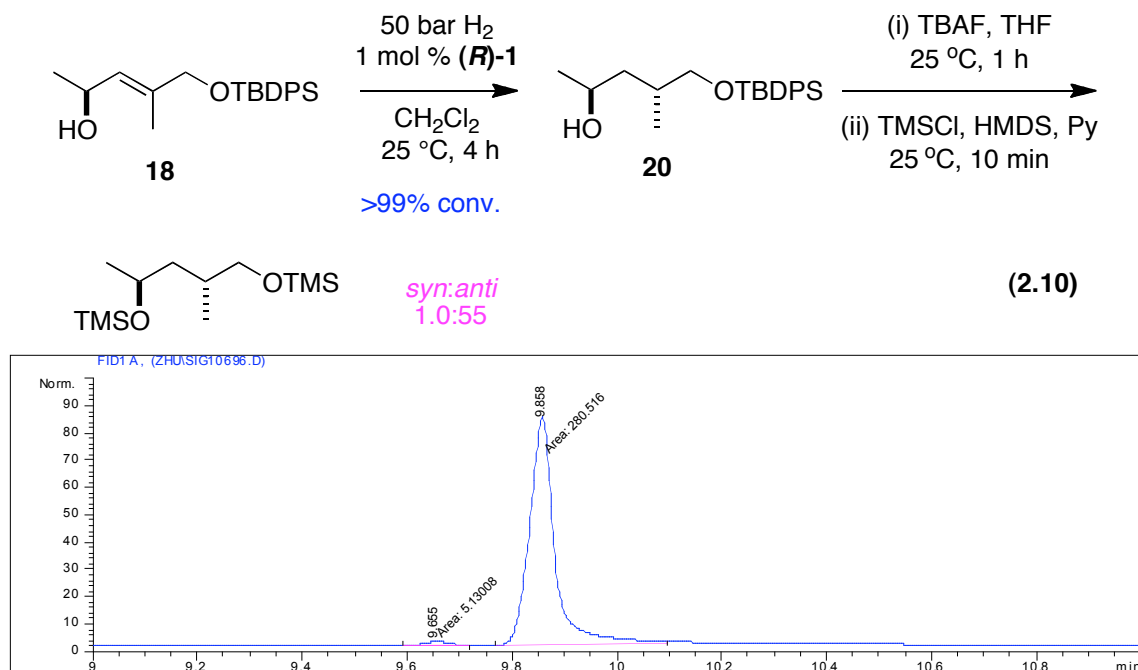
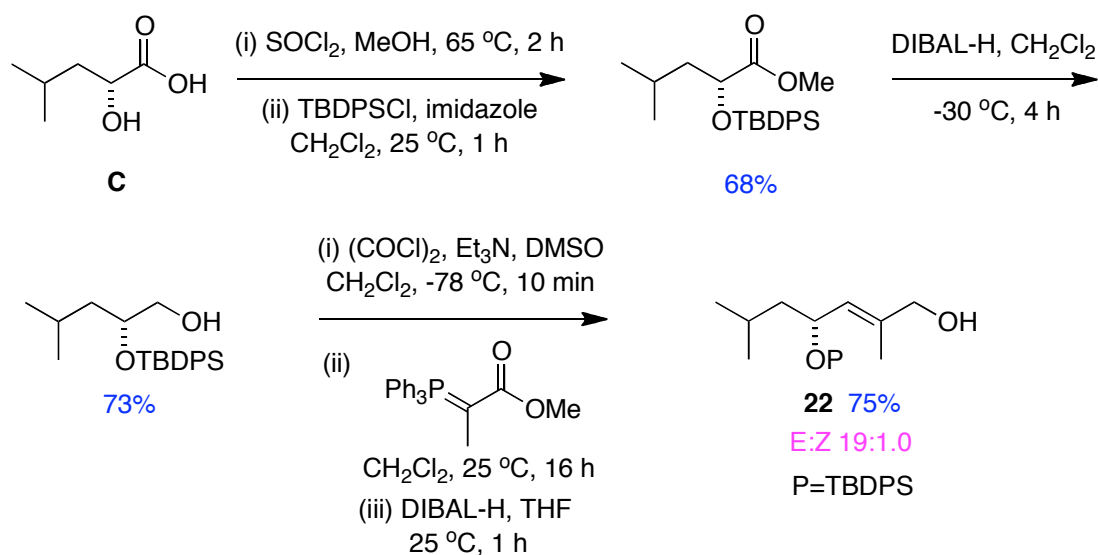


Figure 2.13. GC separation of modified hydrogenation products from **(R)**-**1** catalyzed hydrogenation of **18**.

2.2.4 Total synthesis of (-)-dihydromyoporone

(-)-Dihydromyoporone is a stress metabolite of the furanoterpenoid type, isolated from slices of the root of sweet potato.⁸⁵ A synthesis (-)-dihydromyoporone **21**^{86,87} was performed to illustrate α -hydroxyacids other than lactic could be used to build terminal 1,3-hydroxymethyl chirons. Thus the allylic alcohol **22** was prepared from commercially available (*R*)-2-hydroxy-4-methylpentanoic acid **C** via a series of standard steps. The Wittig reaction provided the desired *E*-enoate with contamination of small amount of *Z*-isomer. After reduction (DIBAL), the pure *E*-allylic alcohol **22** can be obtained with high yield (Scheme 2.4).

Scheme 2.4. Synthesis of olefin substrate **22** for the total synthesis of (-)-dihydromyoporone.



Hydrogenation of **22** under the standard conditions gave the crude alcohol in excellent diastereoselectivity. The *isobutyl*-for-*methyl* substitution that connects Figure 2.5.a with the hydrogenation in Figure 2.14.a had no adverse effect on the stereoselectivity. After flash chromatography, the desired product was isolated in high yield, and the diastereomeric impurity was hardly perceptible by GC. Interestingly, the hydrogenation of **23**, the *Z*-isomer of **22**, gave a even higher selectivity for the anti-isomer of **24** (*syn:anti*, *dr* 1.0:60) (Figure 2.14.b).

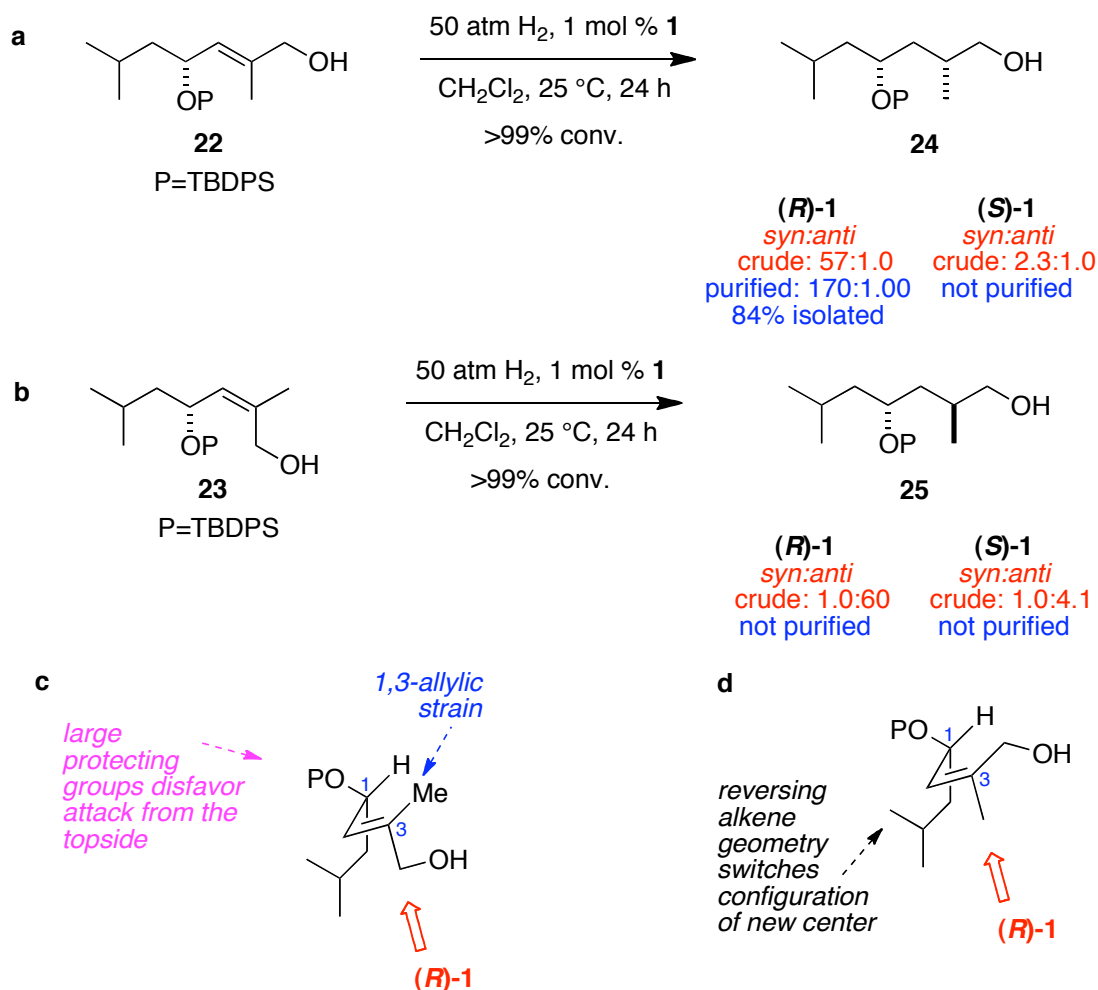
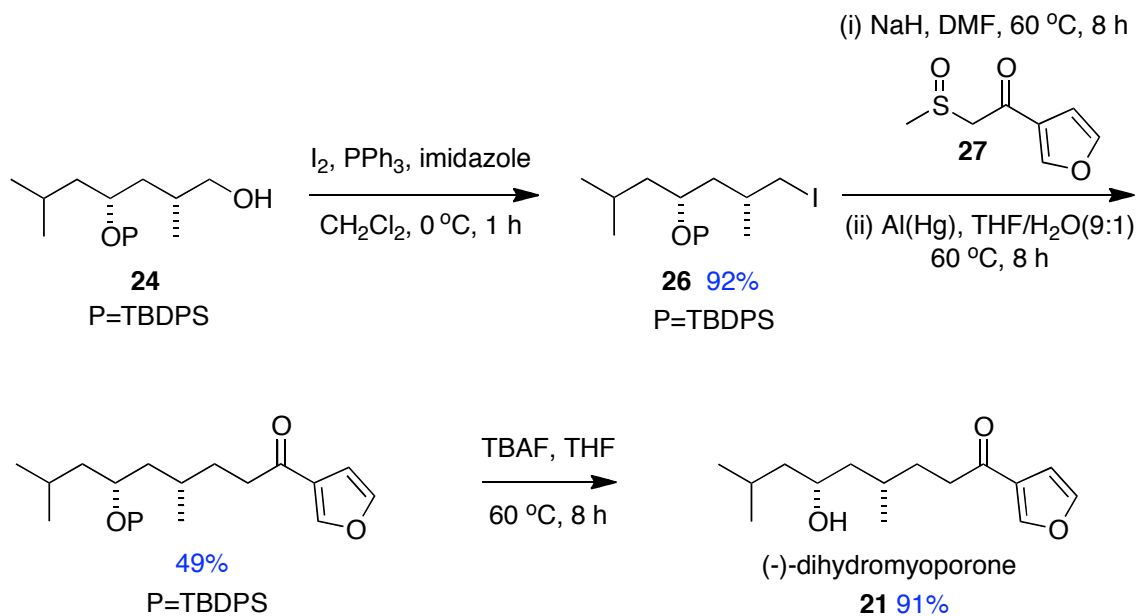


Figure 2.14. **a** Preparation of total synthesis precursor **24** (isolated in 84 % yield and a 170:1.00 *syn:anti* ratio after one chromatographic separation); **b** hydrogenation of *Z*-allylic alcohol **23**; **c** 1,3-allylic strain model. **d** model for substrate **23**; Conversion >99 % throughout. All ratios quoted are from GC.

From the hydrogenation product **24**, the final product (-)-dihydromyoporone **21** can be obtained via formation of the iodide **26**, homologation with sulfoxide **27**, reduction, then deprotection. The ¹H NMR, ¹³C NMR, optical rotation value, HRMS data of the synthetic compound all agreed well with the reported data.

Scheme 2.5. Total synthesis of (-)-dihydromyoporone.

2.3 Conclusions

This chapter attempts to convey several key points. First, constructive matching of chiral Crabtree's catalyst analogs with stereochemical vectors from substrates can afford high diastereoselectivities, even in cases where Ir- or Rh-*diphosphine* complexes would probably give poor conversions and/or selectivities. We have previously observed *catalyst* control dominating hydrogenation of some substrates leading to deoxypolyketides.^{28,77,78} The fact that this is not uniformly so here enhances the scope of the approach; mechanistic complementarities enabled all stereoisomers of the ubiquitous chiral fragments **A** and **B** to be made.

Using the newly developed methodology, (-)-dihydromyoporone was synthesized efficiently. This not only demonstrated that this methodology is highly practical, but also proved that methyl substituent is not necessary for the terminal chirons (can also be *iso*-butyl etc.). To the best of our knowledge, this is the first method that can give all the diastereoisomers of chiron **A** and **B** with high selectivities. We are looking forward to seeing the wide application of this methodology in organic chemistry.

CHAPTER III

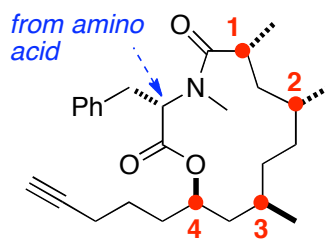
AN ASYMMETRIC HYDROGENATION ROUTE TO (-)-SPONGIDEPSIN*

3.1 Introduction

(-)-Spongidepsin **28** is a natural product isolated recently from a *Spongia* sp. sponge collected off the Vanuatu Islands, Australia, by Riccio and co-workers.⁸⁸ Its cytotoxic and antiproliferative activities against J774.A1, WEHI-164, and HEK-293 cancer cell lines are accompanied by an unprecedented structure. The genus *Spongia* is a well-known source of diterpenoid and polyketide natural products, such as epispongiadiol and spongistatin, respectively. However, **28** reflects a distinct biogenetic origin that combines amino acid and ketide motifs within a 13-membered macrocycle. The ketide domain is comprised of a 9-hydroxy-2,4,7-trimethyltetradeca-14-ynoic acid, while the amino acid was established as (*S*)-*N*-methylphenylalanine by Marfey analysis of the acidic hydrosylate of **28**.^{88,89} The absolute configurations of the other four stereogenic centers were determined by total synthesis.⁹⁰⁻⁹³

Besides the amino acid-derived chirality, there are four stereogenic centers in spongidepsin. Table 3.1 outlines the origin of these chiral centers in the four previous total syntheses of this molecule. As the data shown here, most of the previous syntheses focused on C-C bond formation reactions, which often involve chiral auxiliaries. In two of these syntheses, enzyme-mediated resolutions were used to generate 1,3-dimethyl chirons. For most of these key reactions, the diastereoselectivities were not very good, so alternative methods were sought to increase synthetic efficiency and expose opportunities for analogs syntheses.

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Table 3.1. Comparison of previous syntheses of spongidepsin.

	chiral centers			
	1	2	3	4
Forsyth ⁹¹	enzyme resolution ^a		hydroboration (1.0:1.0)	epoxide opening
Ghosh ⁹²	enzyme resolution		Evan's alkylation (98:2.0)	bromo-lactonization (19:1.0)
Cossy ⁹⁰	Roche ester	crotyl-stannylation (87:13)	asymmetric alkylation (85:15)	SmI ₂ -mediated (85:15)
Negishi ⁹³	ZACA ^b (82 % <i>ee</i>)	ZACA (5.5:1.0)	ZACA (3.5:1.0)	allyl-boration (not specified)

^a Stereoselectivities are not indicated for kinetic resolution steps since they are conversion dependent. ^b ZACA is zirconium-mediated asymmetric carboalumination. There are also two "formal" syntheses of spongidepsin.^{94,95}

Our group has been using chiral analogs of Crabtree's catalyst in syntheses of some pivotal chirons for preparations of natural products, particularly in the polyketide series. This chapter describes how those methods were applied to the preparation of (-)-spongidepsin **28** and some close analogs of this structure.

3.2 Results and discussions

3.2.1 Syntheses of the 1,3-hydroxymethyl chiron

Figure 3.1 illustrates the target molecule containing chirons **29** and **30** that we proposed could be made via stereoselective hydrogenations. To obtain compound **29**, a Sharpless kinetic resolution^{96,97} of the allylic alcohol **31** was used (Scheme 3.1). Acylation, oxidative cleavage, reaction with a stabilized Wittig reagent, then hydride reduction gave the allylic diol **32**.

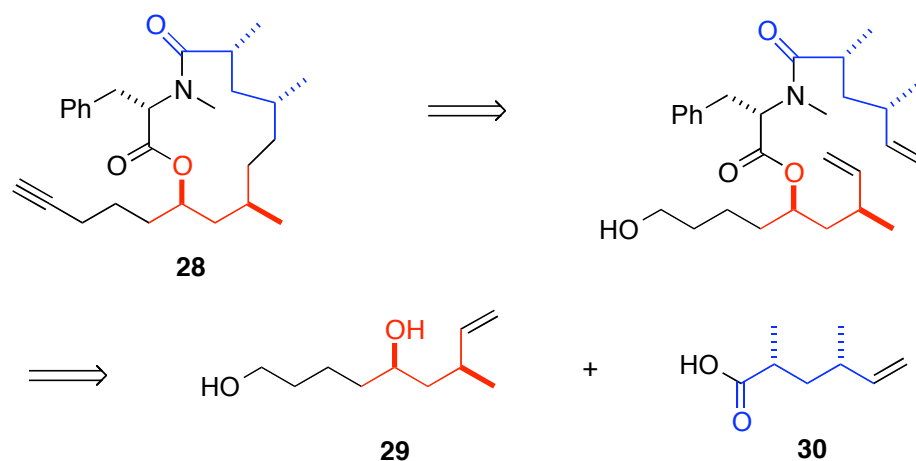
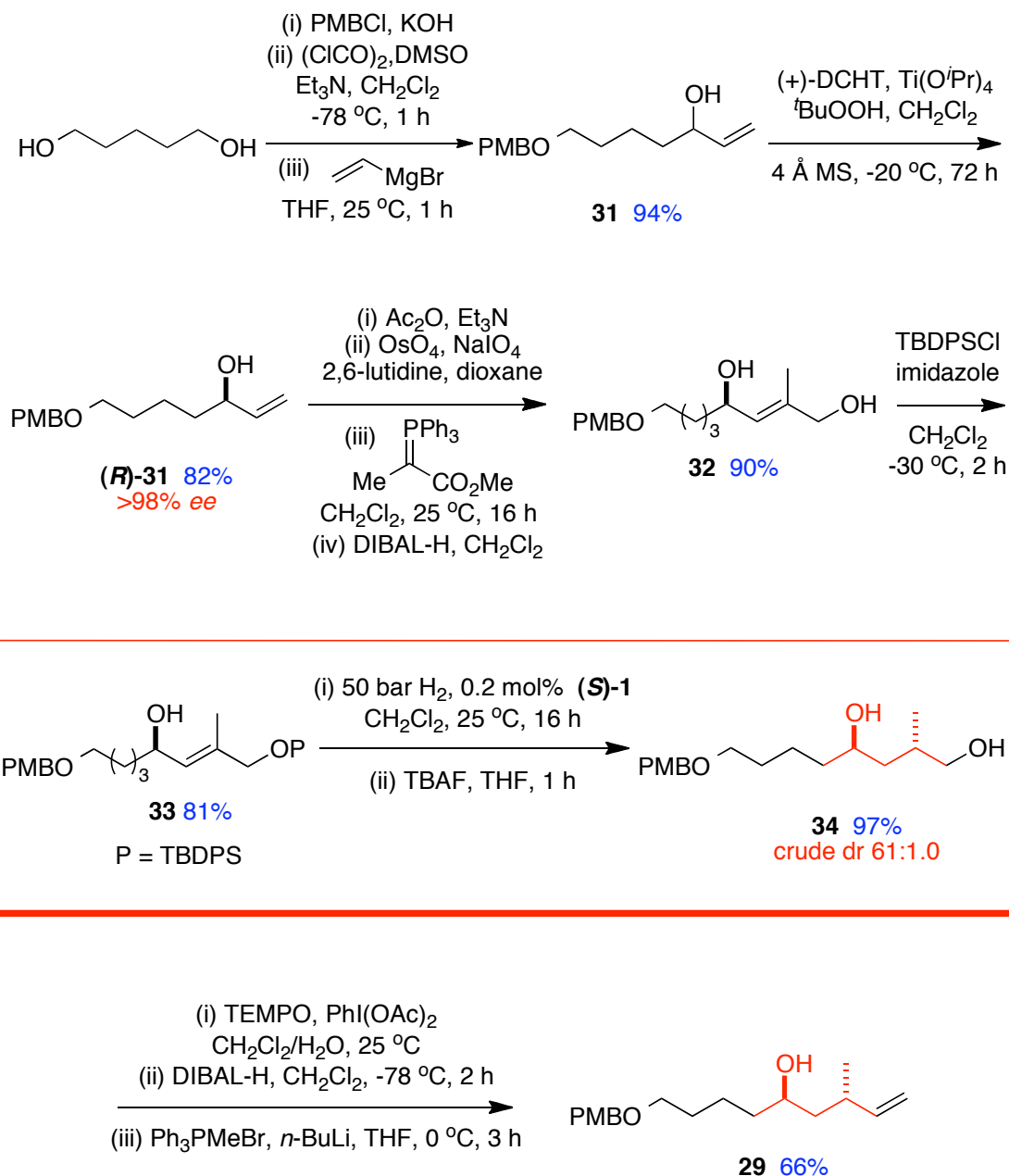


Figure 3.1. Retrosynthesis of **28** highlighting the chirons from stereoselective hydrogenations.

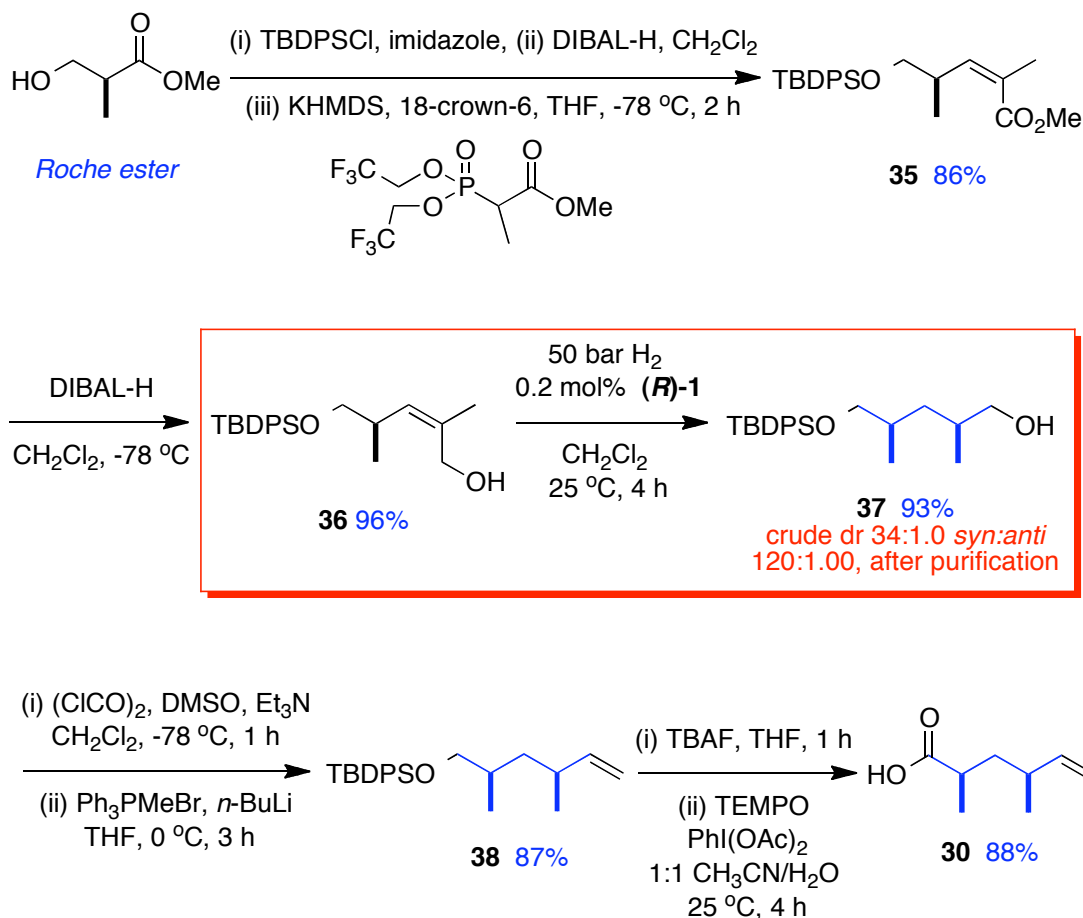
Previous studies from our group have shown that catalyst control tends to prevail in hydrogenations of acyclic chiral substrates^{28,77-79,98,99} using catalysts like our carbene complex **1**. However, manipulation of the alkene component in these reactions provides a means to optimize the “substrate-vector” such that it matches⁵² the catalyst influence to maximize stereoselectivity. This can be done by interchanging ester and alcohol functionalities, altering protecting groups, or changing the alkene geometry. In the case of 1,3-hydroxymethyl chirons, we have shown that an alkene with similar functionality, protection, and geometry relative to **33** was hydrogenated with high stereoselectivity.⁷⁹ The reduction of **33** to **34** occurred with similar high selectivity. Chiron **29** was then generated from **34** via routine oxidation, reduction, and Wittig homologation steps.

Scheme 3.1. Synthesis of the 1,3- hydroxymethyl chiron **29**.

3.2.2 Syntheses of the 1,3-dimethyl chiron

Scheme 3.2 outlines how the second pivotal chiron, **30**, was obtained. Starting from the *Roche ester*, *Z*-allylic alcohol **36** can be made in 4 steps with an 83% overall yield. Hydrogenation of **36** reiterates one of the several reactions we have used to prepare 1,3-dimethyl chirons.^{28,77,78} This reaction is catalyst controlled, but there is a significant “substrate vector”, and the *Z*-allylic alcohol was used to optimize this. Crude material formed in this step had a 34:1.0 *syn:anti* diastereomeric ratio, and 93 % yield of 120:1.0 *syn:anti* product was obtained after one chromatography. The sequence of Swern oxidation, Wittig reaction, silyl deprotection, and alcohol oxidation shown here converting the alcohol **37** to the acid **30** were straightforward transformations.

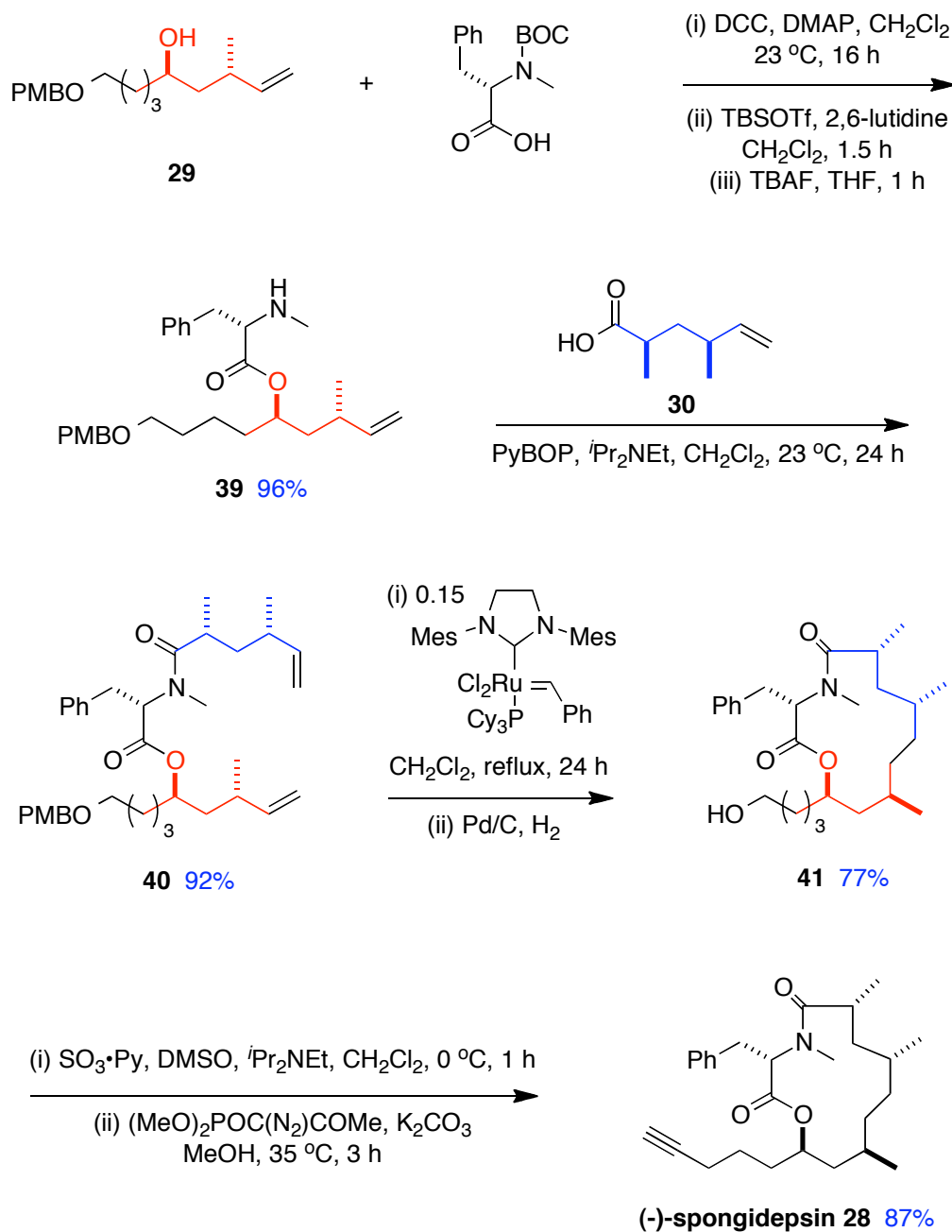
Scheme 3.2. Synthesis of the 1,3-dimethyl chiron **30**.



3.2.3 Coupling of the fragments and completion of the total synthesis

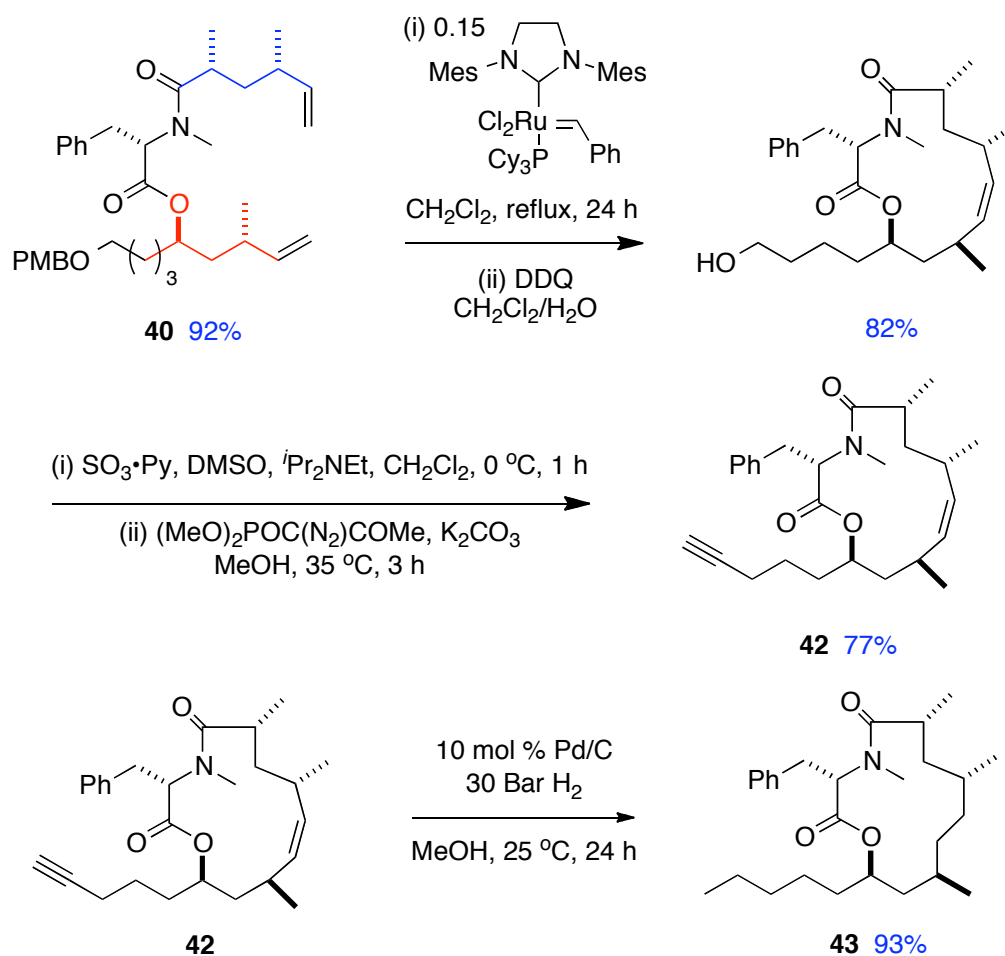
To complete our synthesis of (-)-spongidepsin **28**, chiron **29** was coupled with the appropriate protected *N*-methyl amino acid to give the ester **39** (after removal of the

Scheme 3.3. Completion of the synthesis of **28**.



Boc group). This was then coupled with chiron **30** to form the α,ω -diene **40**. Ring closing metathesis with the “second generation” Grubbs catalyst^{100,101} gave the macrocycle **41** after simultaneous *O*-deprotection and alkene hydrogenation. The final steps in the synthesis were oxidation and generation of the alkyne group (Scheme 3.3). ¹H and ¹³C NMR spectra of the synthetic product **28** compared closely with those reported in previous syntheses.⁹⁰⁻⁹³

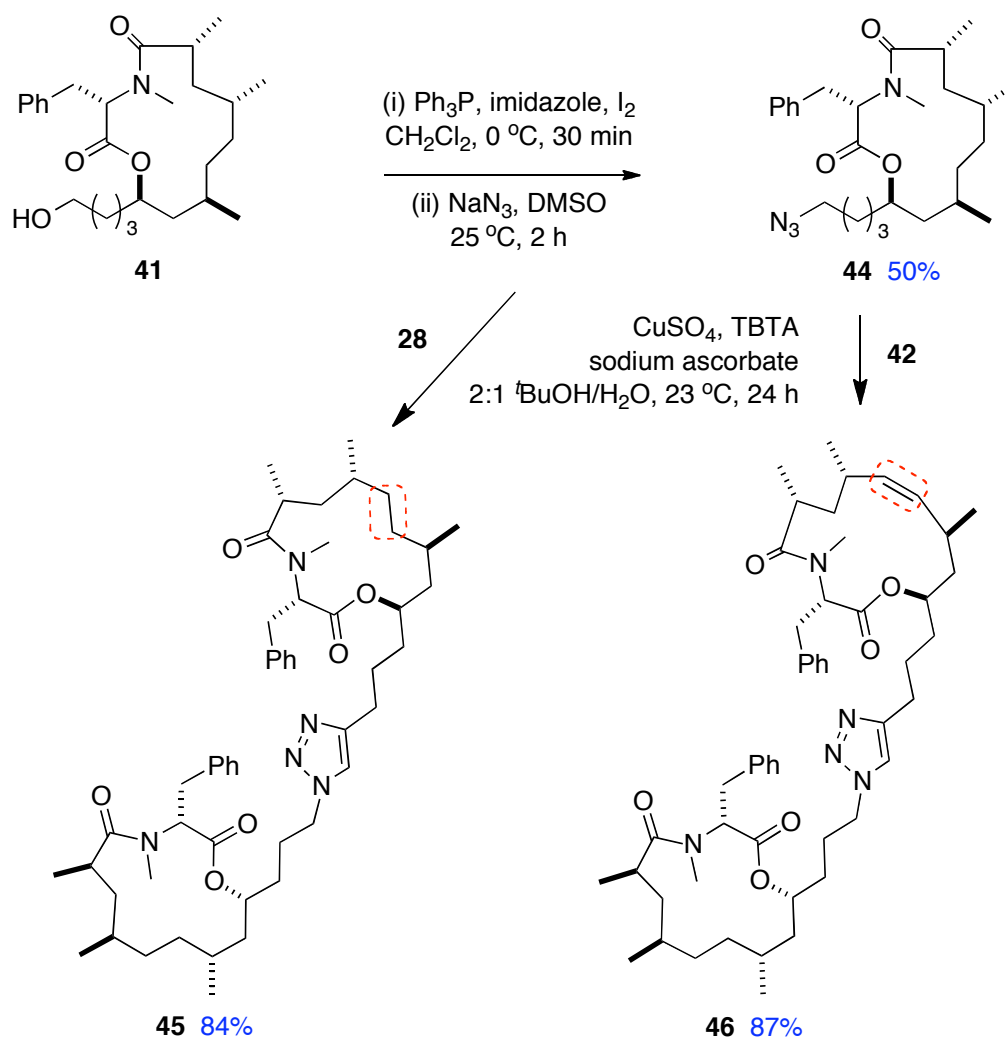
Scheme 3.4. Syntheses of the derivatives of (-)-spongidepsin.



As far as we are aware, nothing has been reported on structure activity relationships for spongidepsin. Consequently, several intermediates in Scheme 3.3 were

diverted to form analogs of the target material for testing. Thus compounds **42** and **43** were also prepared. Starting from intermediate **40**, after ring closing metathesis, instead of reducing the internal double bond, the PMB protecting group was removed with DDQ. The resulting primary alcohol was then transformed to the alkyne **42**, which was an unsaturated derivative of the natural product **28**. Compound **43** could be conveniently obtained via reduction of **42** (Scheme 3.4). Motives for making these particular compounds were to test the effects of increased conformational rigidity in the macrolide, and the effects of saturating the side chain on the cytotoxicity.

Scheme 3.5. Syntheses of the dimers of (-)-spongidepsin.



The cellular target for spongidepsin is unknown. Consequently, we also decided to prepare two bivalent molecules consisting of two macrolide fragments joined by a flexible linker via a “click reaction” (Scheme 3.5).^{102,103} These analogs were designed to probe if this modification would have significant effects on the molecular cytotoxicities; if it did, this might implicate a homodimeric binding partner.

Table 3.2. *In vitro* antiproliferative activity of **28** and derivatives **42**, **43**, **45**, and **46**.

compound	IC ₅₀ (mM) ^a
28	5.68 (0.66) ^b
42	8.27
43	7.32
45	non cytotoxic
46	non cytotoxic
6-mercaptopurine	7.45 (0.007) ^b

^a Assay run for 72 h in EMEM + 2% FBS at 37 °C using human embryonic kidney cells (HEK-293).; ^b Literature data.⁸⁸ IC₅₀ values were measured three times and averaged.

With the help from a postdoc researcher, Aurore Loudet, Compounds **28**, **42**, **43**, **45**, and **46** were tested in an antiproliferative assay on human embryonic kidney (HEK-293) cells (Figure 3.2), and the IC₅₀ values measured are indicated in Table 3.2 relative to 6-mercaptopurine (control cytotoxic compound). These assays were reproduced several times; in our hands the cytotoxicity of compound **28** and of 6-mercaptopurine were both significantly less (one and three orders of magnitude, respectively) than reported previously.⁸⁸ However, the IC₅₀ of 6-mercaptopurine reported in reference 88 is about 100x less than in three other literature reports.¹⁰⁴⁻¹⁰⁶ Further, the relative cytotoxicity of the target compound **28** and 6-mercaptopurine is almost the same. We cannot account for these discrepancies; nevertheless, it is possible to confidently compare the *relative* cytotoxicities of 6-mercaptopurine, **28**, and its analogs in our assays.

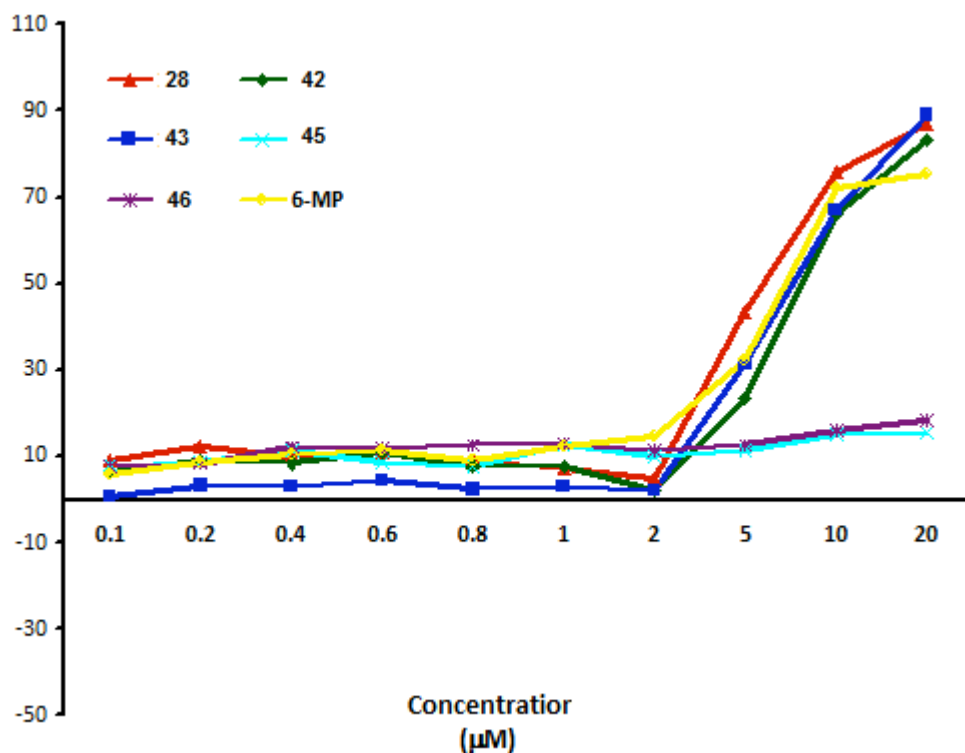


Figure 3.2. Antiproliferative assay for the natural product **28** and the new derivatives **42**, **43**, **45**, and **46** in MTT assays featuring human embryonic kidney cells (HEK-293).

Figure 3.2 indicates that the new monomer derivatives **42** and **43** show little effect up until 2 mM concentrations, after which they are significantly cytotoxic, just as the natural product is. Consequently, reduction of the alkyne side-chain, or incorporation of an alkene in the macrolide has no significant effect. Surprisingly, the bivalent molecules **45** and **46** do *not* show significant cytotoxicities in the same concentration range. Compound **28** and the new derivatives were also tested on human pancreatic carcinoma cells (Panc-1); the IC₅₀ values for the monomers **28**, **42**, **43** were in the same range, and the dimers were also non-cytotoxic (Figure 3.3). Together, these data indicate incorporation of a large substituent on the alkyl chain almost completely eliminates the cytotoxic effect, there was no positive effect from these bivalent analogs.

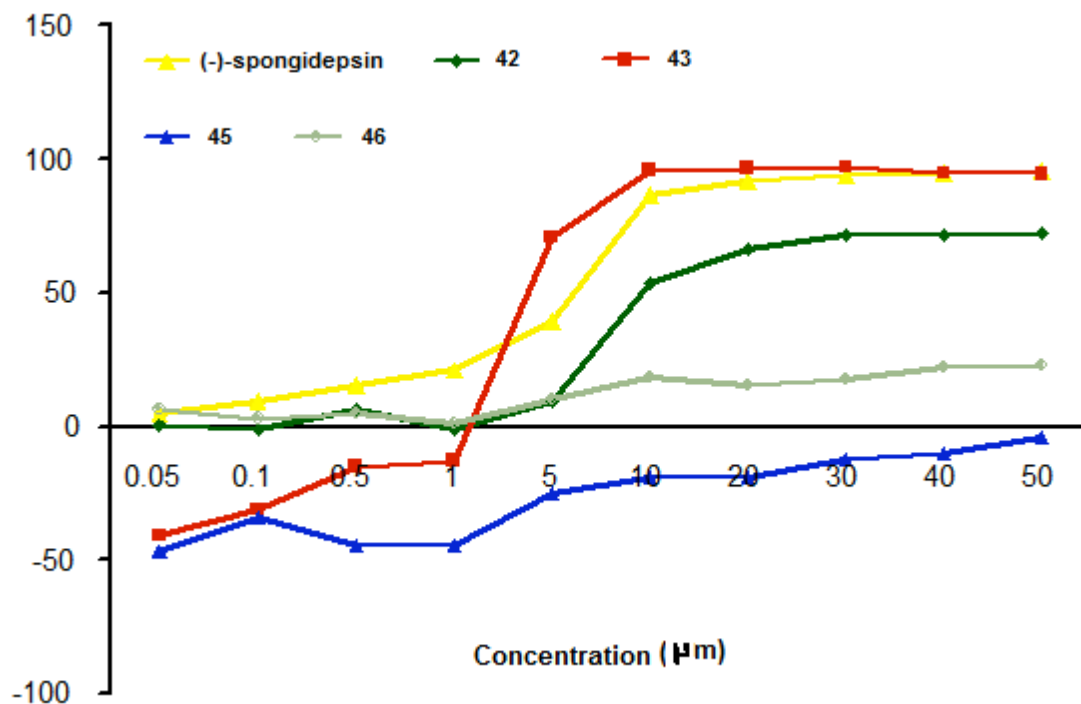


Figure 3.3. Antiproliferative assay for the natural product **28** and the new derivatives **42**, **43**, **45**, and **46** in MTT assays featuring human pancreatic carcinoma cells (Panc-1). Assay were run for 3 days at 37 °C in PFHM-II medium (protein and serum free medium).

3.3 Conclusions

Asymmetric hydrogenations via chiral analogs of Crabtree's catalyst are viable for synthesis of spongidepsin. The results presented here offered some major advantages over previous syntheses. Previous studies from our group indicate all stereoisomers of chirons like **29** and **30** can be made via such methods. We infer from this that stereoisomers of this natural product could be made via similar approaches. The results presented here indicate that practical syntheses of other analog types are also possible. We hope this study can alert synthetic organic chemists to the importance of asymmetric hydrogenations of largely unfunctionalized alkenes in acyclic stereocontrol. We also hope that in the immediate future researchers may use some of the routes to privileged chirons that shown here.

CHAPTER IV

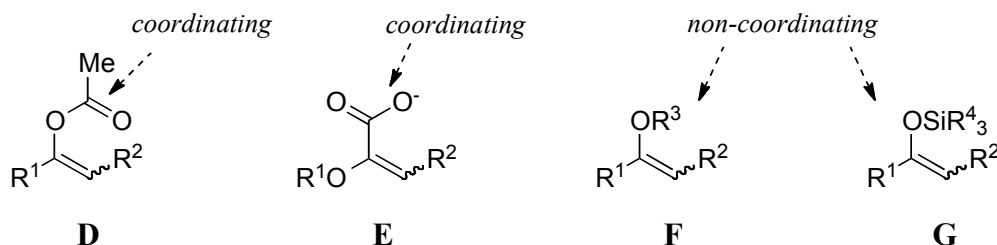
IRIDIUM-CATALYZED ASYMMETRIC HYDROGENATION OF VINYL ETHERS*

4.1 Introduction

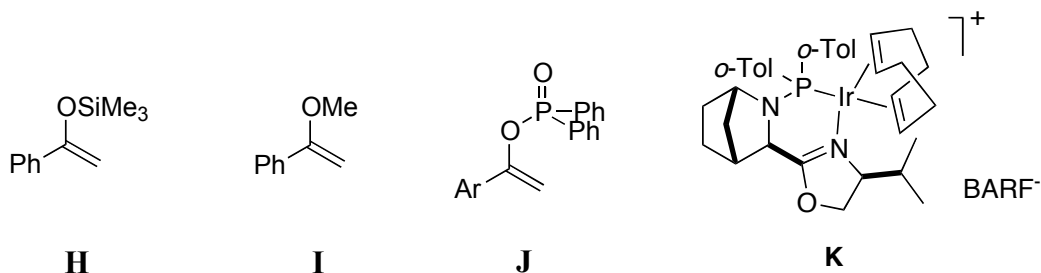
Early interest in the asymmetric hydrogenation of vinyl ethers aimed to find suitable alternatives to the asymmetric hydrogenation of ketones.¹⁰⁷⁻¹¹⁰ However, the hydrogenation of vinyl ethers is not merely a substitute for ketone hydrogenation. Rather, it can lead to products that are difficult or impossible to access directly from the hydrogenation of ketones, such as chiral cyclic ethers. Additionally, some vinyl ethers can also be converted to products other than alcohols. Finally, selective asymmetric hydrogenation of vinyl ether forms a protected chiral alcohol that can be deprotected at any later point in a synthesis.

In our view, alkenes for asymmetric hydrogenations can be divided into three categories.³¹ At one extreme, there are “coordinatively-functionalized alkenes”, that have proximal directing groups that are likely to bind transition-metals in a catalytic cycle. Alkenes with only alkyl substituents are at another extreme; they are completely unfunctionalized. Intermediate between these extremes are “non-coordinatively functionalized alkenes”. These have a proximal functional group that does *not* coordinate to transition-metal catalysts and direct stereofacial modifications. There are more non-coordinative functional groups than coordinative ones, so this intermediate category is the *largest*. It also contains an abundance of precursors to useful chiralons for organic syntheses.

*Reprinted in part with permission from “Carbene-Metal Hydrides Can Be Much Less Acidic Than Phosphine-Metal Hydrides: Significance in Hydrogenations”, Ye Zhu, Yubo Fan, and Kevin Burgess, *J. Am. Chem. Soc.*, **2010**, *132*, 6249-6253. Copyright 2010 American Chemical Society. The pre-peer reviewed version of the following article “Iridium-Catalyzed Asymmetric Hydrogenation of Vinyl Ethers”, Ye Zhu, and Kevin Burgess, *Adv. Synth. Catal.*, 2008, *350*, 979-983.



Asymmetric hydrogenations of enol ethers illustrate the viewpoint outlined above. Enol acetates **D** have a coordinative-functional group: the carbonyl of the acetate, that can transiently bind to a metal center. Consequently, the literature contains many examples of asymmetric hydrogenations of enol acetates, and most of them are quite successful.¹¹¹⁻¹²² α -Aryloxy or α -alkoxy α,β -unsaturated carboxylic acid **E** also has a coordinative-functional group, the carboxyl anion under the basic condition. Recently there are several literature reports about the successful asymmetric hydrogenation of this type of enol ethers too (up to 99.8 *ee* %).¹²³⁻¹²⁶ Conversely, alkylated-, and silylated-enol ethers, **F** and **G** are, by our definition, non-coordinatively functionalized. There are relatively few reports of asymmetric hydrogenations of these, and the enantioselectivities observed have not reached levels that are practical for general application in organic syntheses (alkylated enol ethers,¹²⁷⁻¹²⁹ silylated enol ethers,¹³⁰ furans^{129,131}).

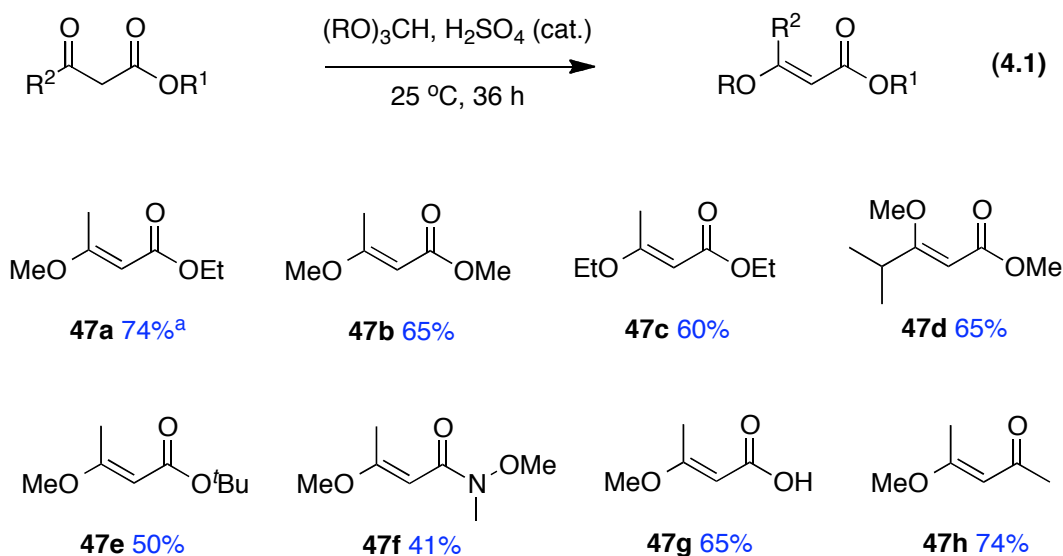


Pfaltz's realization¹¹ that phosphine oxazoline ligands could be used to form chiral analogs of Crabtree's catalyst⁷³ has inspired many researchers. Following his lead, Andersson and co-workers investigated chiral *N,P*-ligated iridium complexes in asymmetric hydrogenations of the silyl- and methyl-enol ethers **H** and **I**, but complex mixtures were obtained using four different catalysts. Subsequently, their study evolved into an investigation of the successful hydrogenations of the enol phosphinates **J** with

catalyst **K**.⁴⁶ Our group was also studying enol ethers as substrates at the time when this research was published. This chapter describes our research results about this study. During this study, we realized that it is quite interesting that catalyst **K** does not work for the simple alkyl enol ethers but the structure similar **1** does. A hydride intermediate acidity difference theory was proposed for this phenomenon based on DFT calculations and some experiment results. This chapter will also talk about these studies in detail.

4.2 Asymmetric hydrogenation of vinyl ethers

4.2.1 Syntheses of the vinyl ethers



a. 1 eq. CaCl_2 was used.

Figure 4.1. Synthesis of vinyl ether ester and its' relative derivatives.

The vinyl ether esters can be made from acetoacetate and orthoformate by using catalytic amount of H_2SO_4 .¹³² Usually to avoid the ester scrambling, the R^1 group in the acetoacetate and the R group in orthoformate should be same (for example **47b**, **47c**, and **47d**). However, by adding anhydrous CaCl_2 , this scrambling can be suppressed since the by-product MeOH can be trapped by the CaCl_2 (**47a** was obtained with 74% yield).

Starting from the **47b**, a series of derivatives can be made via Wenireb amide formation (**47f**), ester hydrolysis (**47g**), and ester formation (**47e**) (Figure 4.1).

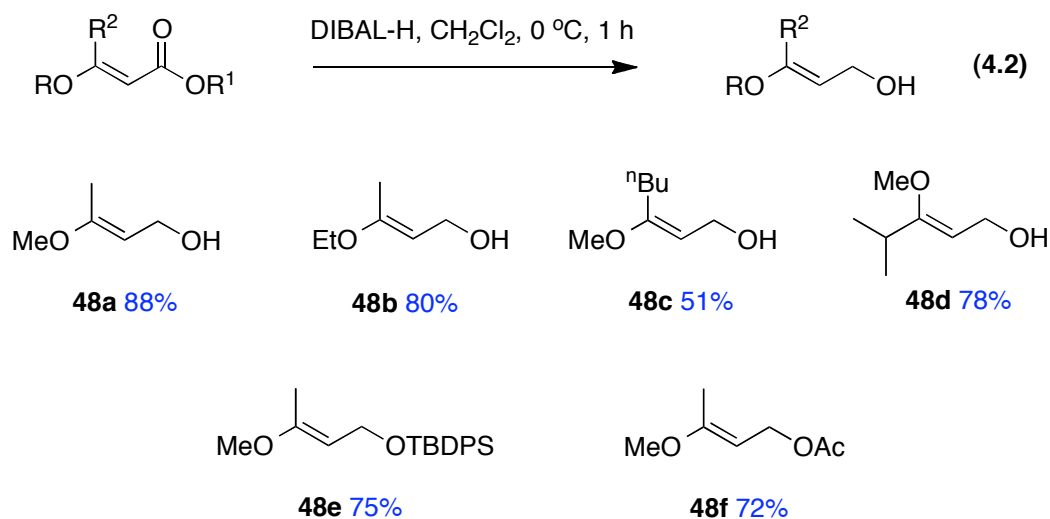
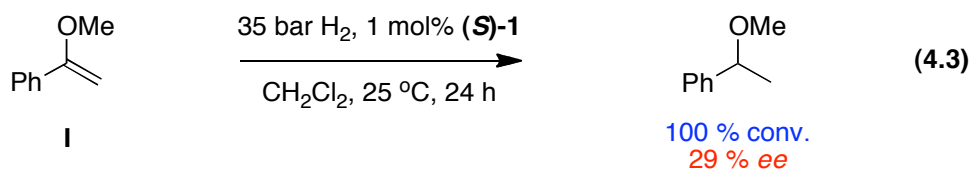


Figure 4.2. Synthesis of vinyl ether alcohols and its' relative derivatives.

With these vinyl ether esters in hand, the vinyl ether alcohols can be easily made by reducing the ester functional groups with DIBAL-H. The vinyl ether alcohols are much more acid sensitive than the vinyl ether esters. Flash chromatography with silica gel (with or without Et₃N) and reduced pressure distillation both gave decomposed products. Finally it was found that flash chromatography with the basic Al₂O₃ can afford the desired product with good isolated yield and purity (Figure 4.2).

4.2.2 Asymmetric hydrogenation of the vinyl ethers



Reaction 4.3 shows the first hydrogenation of an enol ether studied in our laboratories. 1-Methoxy-1-phenylethene (**I**) was reduced *exclusively* to the product using the carbene oxazoline catalyst (**S**)-1. The low enantioselectivity observed for this particular substrate was not a concern because there are many routes to chiral aryl(1-hydroxyethyl) compounds. On the other hand, the high conversion to one single product obtained with the carbene-oxazoline catalyst **1** contrasted with the poor results reported for similar *N,P*-ligands, and provided motivation to investigate substrate scope.

Table 4.1. Optimization of hydrogenation conditions for substrate **47a**.

47a

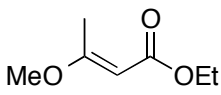
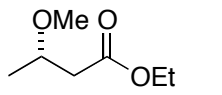
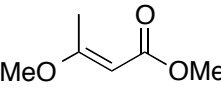
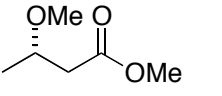
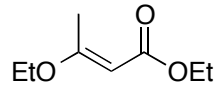
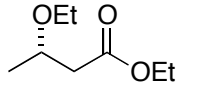
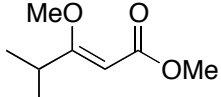
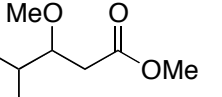
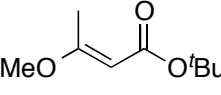
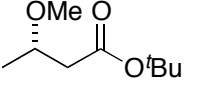
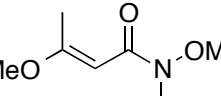
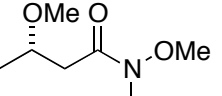
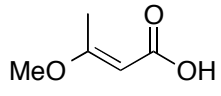
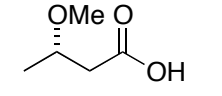
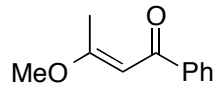
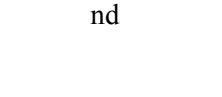
Entry	Temp. (°C)	Pressure (bar)	Time (h)	Conv. ^a (%)	Ee ^b (%)
1	25	5	24	<5	5
2	25	50	24	81	78
3	25	100	24	82	79
4	25	50	48	>99	78
5	50	50	12	95	73
6	-20	50	12	30	83
7	25	50	12	95	77 ^c
8	25	50	12	68	83 ^d

^a Determined by ¹H NMR; ^b Determined via chiral GC; ^c Catalyst loading, 5 mol %; ^d Catalyst loading, 0.2 mol %.

The enol ether **47a**, available from the corresponding ketoester and trimethylorthoformate, was selected as a substrate for further studies and optimization of reaction conditions (Table 4.1). Hydrogen pressures greater than 5 bar were shown to be necessary, but increasing from 50 to 100 bar had no productive effect (entries 1 – 3). Complete conversion was observed when the reaction time was extended to 48 from 24 h (entry 4). At 50 °C the reaction proceeded faster but the enantioselectivity decreased (entry 5). Conversely, a slightly higher enantioselectivity was observed at -20 °C but the conversion was poor (entry 6). Entries 7 and 8 show that a slightly higher enantioselectivity was observed at a lower catalyst loading, but the conversion was less

reflecting a slower reaction rate. On the basis of these observations, the conditions used in entry 4 were selected for application to different substrates.

Table 4.2. Asymmetric hydrogenation of vinyl ether esters.

$ \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2\text{O}-\text{C}=\text{C}-\text{C}(=\text{O})\text{OR}^3 \\ \text{47} \end{array} \xrightarrow[\text{CH}_2\text{Cl}_2, 25\text{ }^\circ\text{C}, 48\text{ h}]{50\text{ bar H}_2, 1\text{ mol\% (S)-1}} \begin{array}{c} \text{R}^1 \\ \\ \text{R}^2\text{O}-\text{CH}-\text{CH}_2-\text{C}(=\text{O})\text{OR}^3 \\ \text{49} \end{array} $			
47	Conv. (%) ^a	Ee (%) ^b	49 ^c
 47a	>99	78	 49a
 47b	85	60	 49b
 47c	>99	66	 49c
 47d	15	nd ^d	 49d
 47e	>99	88	 49e
 47f	90	90	 49f
 47g	>99	63	 49g
 47h	<5	nd ^e	 49g nd

^a Determined by ¹H NMR; ^b Determined via analysis on a chiral GC column; ^c Stereochemical assignments via reduction of the hydrogenation products to primary alcohol then comparison with authentic samples; ^d Assignment of the absolute configuration of the product was not made; ^e *E/Z* isomerization occurs during the reaction and most of the starting material remains.

Table 4.2 shows hydrogenations of similar substrates **47a** – **h** at 48 h reaction time. High conversions could be achieved for esters **47a** – **c** where the substituents are not large, but the *iso*-propyl substituted enol ether **47d** gave only 15 % conversion in the first 48 h of the reaction. When the size of the ester group in this series was increased to *tert*-butyl as in substrate **47e**, the enantiomeric excess increased significantly. The *N*-methoxy amide **47f** was a good substrate for this reaction; it gave a high conversion and the best enantiomeric excess in the series. However, the enantioselectivity for the corresponding acid **47g** was significantly diminished. Finally, the phenyl ketone **47h** was not hydrogenated quickly under these conditions and *E/Z*-isomerization of the alkene was observed.

DIBAL reduction of the ester **47c** gave the allylic alcohol **48b**. However, when this was hydrogenated under the conditions specified in Table 4.2 (and Table 4.3, entry 1), the ketone **51** was formed in preference to the desired ether **50b**. One explanation for this by-product is protonation of the hydroxyl group, elimination to an enone, then hydrogenation. Indeed, entries 2 – 4 in Table 4.3 show that progressively higher amounts of anhydrous potassium carbonate enhance the chemoselectivity of the reaction in favor of the hydrogenation product **50b**, and the *ee* values throughout were excellent. It was also observed that when 4Å molecular sieves were used (and *no* potassium carbonate), then **50b** could also be the major product (data not shown).

Table 4.3. Optimization of the hydrogenation conditions to avoid ketone formation.

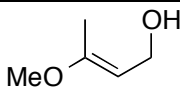
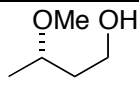
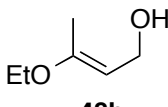
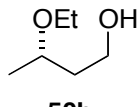
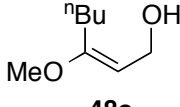
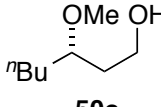
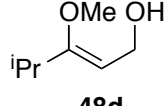
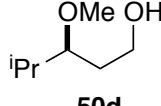
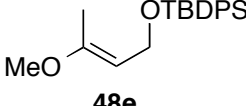
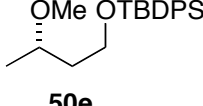
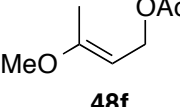
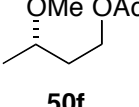
CCOC(=C)CO (**48b**) $\xrightarrow[25\text{ }^{\circ}\text{C}, 12\text{ h}]{50\text{ bar H}_2, 1\text{ mol\% (S)-1, K}_2\text{CO}_3, \text{CH}_2\text{Cl}_2}$ CCOC[C@H](CO)CC (**50b**) + CC(=O)CC (**51**)

>99 % conv.
>98 % *ee*

Entry	K ₂ CO ₃ (mol %)	50b : 51 ^a
1	0	30:70
2	20	67:33
3	30	83:17
4	50	>99:1.0

^a Determined by ¹H NMR.

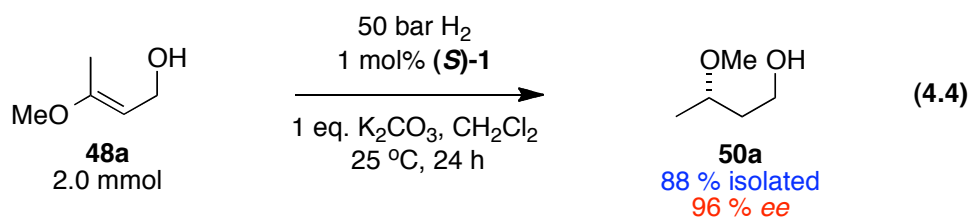
Table 4.4. Asymmetric hydrogenation of vinyl ether alcohols.

$ \begin{array}{c} \text{R}^1 \quad \text{OR}^3 \\ \diagup \quad \diagdown \\ \text{R}^2\text{O}-\text{C}=\text{C}-\text{CH}_2\text{OH} \\ \mathbf{48} \end{array} \xrightarrow[1 \text{ eq. K}_2\text{CO}_3, \text{CH}_2\text{Cl}_2, 25^\circ\text{C}, 12 \text{ h}]{50 \text{ bar H}_2, 1 \text{ mol\% (S)-1}} \begin{array}{c} \text{OR}^2 \quad \text{OR}^3 \\ \quad \\ \text{R}^1-\text{CH}_2-\text{CH}_2-\text{OH} \\ \mathbf{50} \\ >99\% \text{ conv.} \end{array} $		
48	Ee (%) ^a	50^b
 48a	96	 50a
 48b	98	 50b
 48c	93	 50c
 48d	91	 50d
 48e	89 ^c	 50e
 48f	92 ^c	 50f

^a Determined via analysis on a chiral GC column; ^b Stereochemical assignments were made via comparison with authentic samples; ^c K₂CO₃ was not required in this case.

The observations outlined above led us to broaden the substrate scope to include those shown in Table 4.4. Substrates **48a** and **48b** have methyl-to-ethyl relationships, and this change did not significantly alter the enantioselectivities observed. The enantioselectivity reduced only very slightly when the alkene methyl-substituent was replaced with an *n*-butyl group as in substrate **48c**. Substrate **48d** has a *Z*-stereochemistry and a more bulky substituent (*i*Pr). For this compound the enantioselectivity observed was also high, and the catalyst approached the alkene from the same face effectively giving an inverted stereochemistry because the alkene

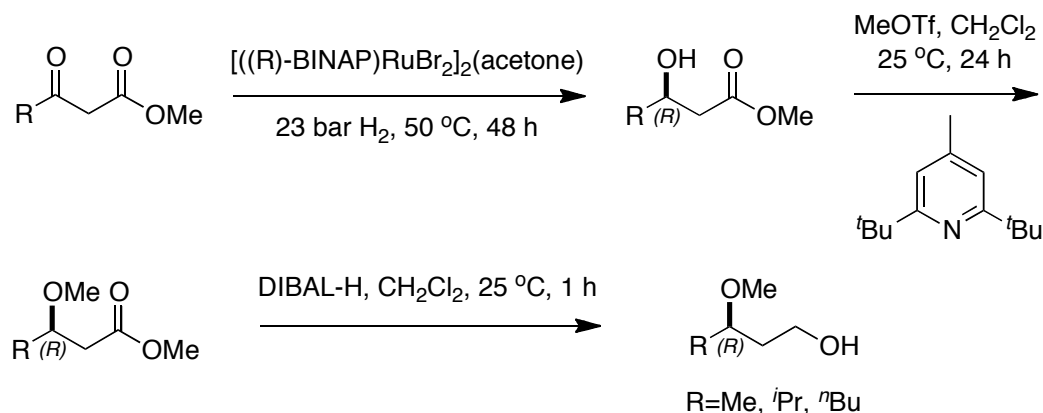
geometry was reversed. Hydrogenation of substrate **48e** compared with the corresponding alcohol **48a** indicates that the catalyst approaches the alkene from the *same* direction for the silylated substrate, and high enantiomeric selectivity is maintained. Similarly the acetate **48f** was hydrogenated with good enantioselectivity and from the same face. Potassium carbonate was *not* required to obtain high conversions with the protected alcohols **48e** and **48f**. Conversions were very high throughout this series and the reaction was faster than for the corresponding esters shown in Table 4.2.



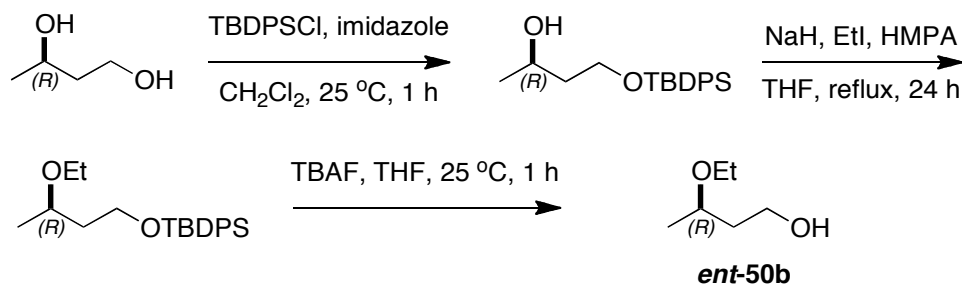
Finally, reaction 4.4 was performed on a slightly larger scale than those shown in Table 4.4. The product of this reaction **50a** was isolated in high yield via column chromatography.

4.2.3 Absolute configuration determinations

The absolute stereochemistry of the hydrogenation products was determined via comparison with the known compounds that were made via the asymmetric hydrogenation of acetoacetate with Noyori's type catalyst. The *R* type chiral ethers can be made through the route shown in Scheme 4.1. By comparing the GC retention time of these prepared ethers with the products from iridium catalyzed hydrogenation of vinyl ethers, it is clear that hydrogenations with (**S**)-**1** provided *S* type chiral ethers for the **50a**, **50c**, **50e**, and **50f**. For (*Z*)-vinyl ether alcohol **48d**, (**S**)-**1** provided *R* type chiral ether **50d**.

Scheme 4.1. Synthesis enantiomer enriched chiral ethers.

Starting from commercial available (*R*)-1,3-butanediol, the enantiomeric enriched ether **ent-50b** can be synthesized through route shown in Scheme 4.2. By comparing the GC retention time of **ent-50b** with hydrogenation product, the stereochemistry of **50b** can be determined to be *S*.

Scheme 4.2. Synthesis enantiomer enriched **ent-50b**.

Finally, the stereochemistry of the **49a-g** can be determined by reducing to the alcohols, and then compared with the geometry already known chiral alcohols **50a-f** via GC.

4.3 Metal hydrides acidity studies

4.3.1 Background

Transition-metal hydrides are ubiquitous in catalysis.¹³³ They are frequently formed as intermediates even in cases where the catalyst precursor does not contain a M-

H bond, and they may also be formed *en route* to catalyst deactivation. The reactivity of transition-metal hydrides is widely variable. Different coordination modes are open to hydride (and dihydrogen) ligands, they may dissociate to donate hydrides or protons, and they can participate in hydrogen bonding.^{81,134} In some cases the importance of metal hydrides in catalysis is obvious. In most Heck couplings,¹³⁵ for instance, transition-metal hydrides reductively eliminate acidic molecules, hence it is necessary to add a base to avoid complications that would be caused by accumulation of acid. In the rhodium catalyzed hydrogen-mediated reductive aldol coupling reaction, addition of base is also necessary to suppress the undesired 1,4-reduction pathways.¹³⁶ In other cases, basic additives have equally profound effects but the underlying reasons may be obscure. For instance, some asymmetric homogeneous hydrogenation reactions give significantly better enantioselectivities in the presence of base for non-evident¹³⁷ or undefined¹³⁸ reasons. Acidities of transition-metal hydrides¹³⁹ therefore must also account for some obscure ligand effects;¹⁴⁰ in other words, ligands complexed to metal centers influence the acidities of transition metal hydrides, and this in turn can impact catalysis.

Despite the considerations outlined above, there is a tendency to regard homogeneous catalytic alkene hydrogenations as pH *neutral* because the starting materials, dihydrogen and alkene, are not acidic. Some hydrogenations may be described as “ionic”^{107,108,141,142} because heterolytic cleavage of hydrogen occurs; however, to the best of our knowledge, there are few reports that have commented on how activation of hydrogen with transition metal catalysts impacts the pH of the medium in catalytic transformations. Matsuda and co-workers reported that allylic alcohols could be substituted by various nucleophiles when treated with $[\text{Ir}(\text{cod})(\text{PPh}_3)_2]\text{PF}_6$ that had been activated by H_2 . They suggested that the reaction proceeded via activation of the alcohol to give an allylic cation that was subsequently attacked by the nucleophile to give the final product. In control experiment, Matsuda observed similar reactivity using a catalytic amount of $\text{CF}_3\text{SO}_3\text{H}$ instead of the iridium catalyst.¹⁴³ In both Andersson¹⁴⁴ and Pfaltz’s¹⁴⁵ asymmetric hydrogenation work, they found that their Ir-*N,P* catalysts are not suitable for some very acid sensitive substrates. In some of Krische’s rhodium

catalyzed hydrogen-mediated C-C bond formation reactions, base was found to be necessary for high yields of the desired coupling products.^{136,146}

The research study presented here further demonstrates that catalytic hydrogenation reactions need not be intrinsically neutral, and this can be extremely significant to the products formed. Specifically, we draw attention to iridium-mediated hydrogenations of alkenes by analogs of Crabtree's catalyst $[(\text{COD})\text{Ir}(\text{PCy}_3)(\text{py})]^+$ as a situation in which significant concentrations of protons may be generated. Further, the outcome of these hydrogenation reactions can be affected by the acidities of catalytic intermediates.

4.3.2 DFT calculations about the $\text{p}K_{\text{a}}$'s of the metal hydride intermediates

Direct experimental evidence for the mechanism of hydrogenations by Crabtree's catalyst analogs is unavailable, and difficult to obtain via kinetic or spectroscopic methods.^{24,26,147} However, calculations first by Andersson³⁰ on a simplified system with an *N,P*-ligand set, then from our laboratories^{24,29} on the carbene-oxazoline complex **1** converge on very similar preferred reaction pathways. This involves loss of the COD ligand, and complexation with the alkene substrate and two molecules of dihydrogen. The rate-limiting step in the catalytic cycle is transformation of this tetrahydride **L** into the *s*-alkyl species **M** (Figure 4.3).

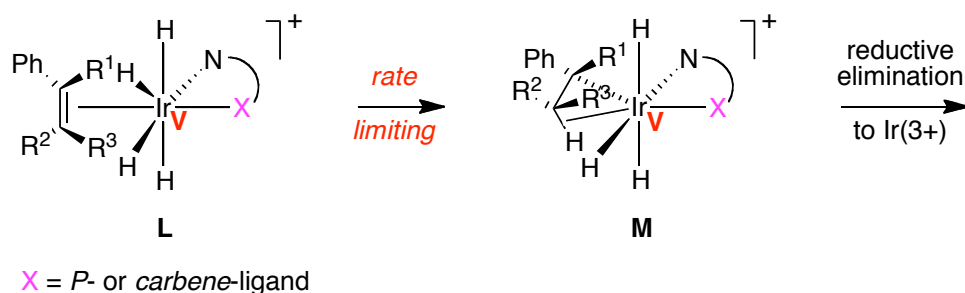


Figure 4.3. Postulated turnover limiting step in hydrogenations with Crabtree catalyst and analogs.

This mechanism involves alternation between iridium(III) and (V) oxidation states. It indicates why Crabtree's catalyst analogs are able to hydrogenate "coordinatively unfunctionalized" tri- and tetra-substituted alkenes whereas rhodium complexes like Wilkinson's catalyst do not. Specifically, the positively charged and higher oxidation state Ir-complexes are more electrophilic than neutral, and lower oxidation state Rh-complexes, so they have more affinity to the π -electron density of alkene substrates. Moreover, the small steric demands of a tetrahydride ligand set facilitate coordination of alkenes with three or four substituents that are intrinsically hindered. Finally, hydrogenations with these Ir-complexes are *not* particularly sensitive to oxygen, as expected for high oxidation state Ir-intermediates. Involvement of intermediates **L** also explains why the catalytic cycle is so hard to follow spectroscopically because these tetrahydrides are in a rapid, dynamic equilibrium with dihydrido-dihydrogen complexes.^{24,29}

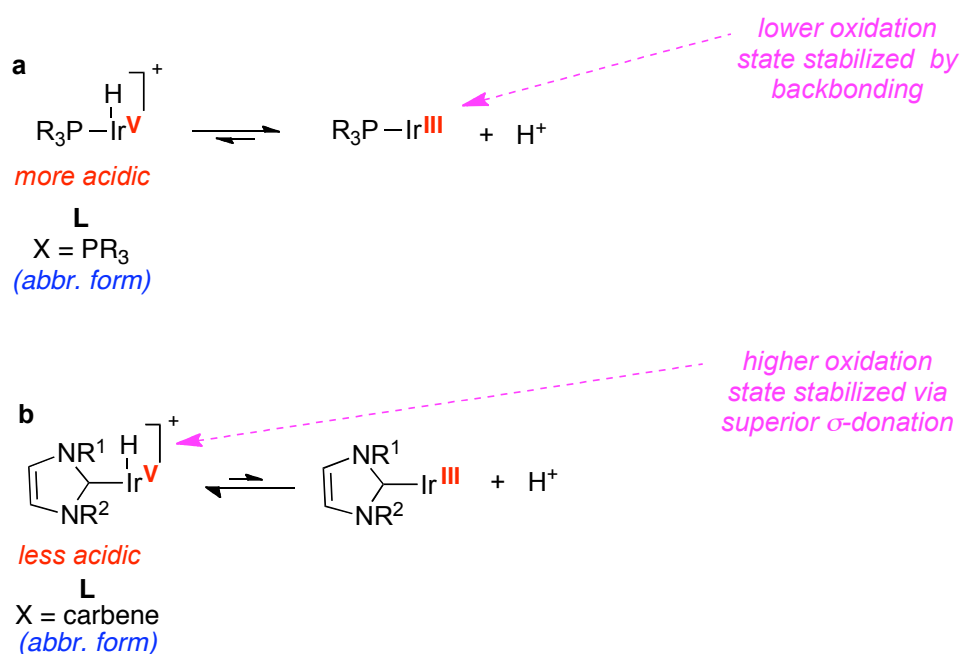


Figure 4.4. Postulate for acidities of **a** the *P*-Ir-H complexes relative to **b** carbene-Ir-H systems.

Figure 4.4 contrasts the factors driving dissociation of protons from the iridium(V) intermediates **L** (shown in abbreviated form) where the ligating group X is either a phosphine or an *N*-heterocyclic carbene intermediate. In both cases, an iridium(III) species forms, *ie* the metal is reduced as its electron density increases. We postulate that this dissociation is *easier when X is a P-ligand than a carbene* because *P*-ligands are: (i) inferior σ -donors hence are less able to stabilize Ir(V);¹⁴⁸ and, (ii) superior π -acceptors thus better able to stabilize Ir(III). Consequently, Crabtree's catalyst and *P*-ligated derivatives should be *more acidic than the corresponding carbenes*.

Table 4.5. pK_a values for transition metal hydrides.

complex		pK _a			
		MeCN		CH ₂ Cl ₂	
		exp	calc ^a	ΔpK_a^b	ΔpK_a^b
1	[HNi(dmpe) ₂] ⁺	24.4±0.2	21.7	11.9	13.4
2	[HPt(dmpe) ₂] ⁺	31.1	32.3	22.5	24.0
3	[HNi(dppe) ₂] ⁺	14.7±0.3	13.8	4.0	5.5
4	[HPt(dppe) ₂] ⁺	22.2	24.6	14.8	16.3
5	N	-	11.3	1.5	1.4
6	O	-	9.8	0	0
7	P	-	11.5	1.7	1.8
8	Q	-	17.4	7.6	7.4
9	R	-	36.1	26.3	30.0

^a Experimental pK_a of Ni and Pt complexes as references, and all have a standard deviation of ± 2.2 ; ^b calculated relative pK_a and set the catalyst intermediate **O** as reference.

Dr. Yubo Fan helped us to use density functional theory (TPSS functional)¹⁴⁹ to calculate acidity differences for the key metal hydride complexes involved in hydrogenations with Crabtree's catalyst analogs, These data were then compared to

reference systems to estimate absolute pK_a values.¹⁵⁰ Almost all reliable experimental pK_a 's for metal hydrides in the literature are measured in acetonitrile, so the calculated pK_a 's were first obtained by simulating reactions in this medium.

In validation work, calculations were performed for several metal hydrides for which pK_a 's have been measured in MeCN (Table 4.5, entries 1 – 4). The calculated pK_a differences were then related to absolute pK_a values using the literature experimental data for each of the other three metal hydride controls, then averaged to give the data shown in Table 4.5, entries 1 – 4. These numbers are consistent with the experimental data with a maximum deviation of 2.7 for entry 1, which concerns a complex of pK_a 21.7. This close agreement for the control complexes indicates a high degree of confidence for application of the same technique to calculate acidities for the key intermediates in hydrogenations by Crabtree's catalyst analogs.

Calculated data for the hydrogenation intermediates are shown in Table 4.5, entries 5 – 9. Considering first the data in MeCN, Crabtree's catalyst **N** was calculated to be less acidic than the *P*-oxazoline complex **O**, so the latter was used as a "bottom-line reference". The *N,P*-ligands in **O** and **P** are alike, hence these complexes would be expected to have similar acidities, and the calculations are consistent with this. Moreover, higher acidity for the diphenylphosphinite complex **O** relative to **P** was also predicted because the diphenylphosphine in **P** is a superior σ -donor, better able to stabilize Ir(V); again, the calculations support this (Figure 4.5).

The most important comparison in Table 4.5 is between the data for the *N,P*-complexes **O/P**, and the corresponding carbene **Q**. Hydrides **O** and **P** were calculated to be 7.6 to 5.9 pK_a units *more* acidic than the carbene intermediate **Q**, as predicted from the concepts outlined in Figure 4.4. A 7.6 pK_a difference is similar to the acidity difference between formic acid and ^tBuOH.

Finally, it is interesting to compare intermediates from Crabtree's and Wilkinson's catalysts. The hydrogenation intermediate **R** from Wilkinson's catalyst was far less acidic than that from any of the iridium complexes. It was 26.3 pK_a units less

acidic than **O** and 24.8 pK_a units less acidic than the tetrahydride **N** from Crabtree's catalyst.

All the calculations discussed so far are for acetonitrile solvent, but hydrogenation reactions with Crabtree's catalyst analogs are generally run in *dichloromethane*. No pK_a data for useful control metal hydrides in dichloromethane has been published; hence calculated pK_a values in that medium cannot be related to absolute values. However, pK_a *differences* between the complexes *are* accessible, and that data is shown in the right hand column of Table 4.5., relative to the intermediate that was calculated to be the most acidic, *ie* the diphenylphosphinite oxazoline **O**. The calculated acidity differences for complexes **N** – **R** in dichloromethane (right hand column) are very similar to those for acetonitrile (penultimate column). This indicates that the differences in pK_a values for the complexes are preserved, no matter how the absolute pK_a values vary between these two solvents.

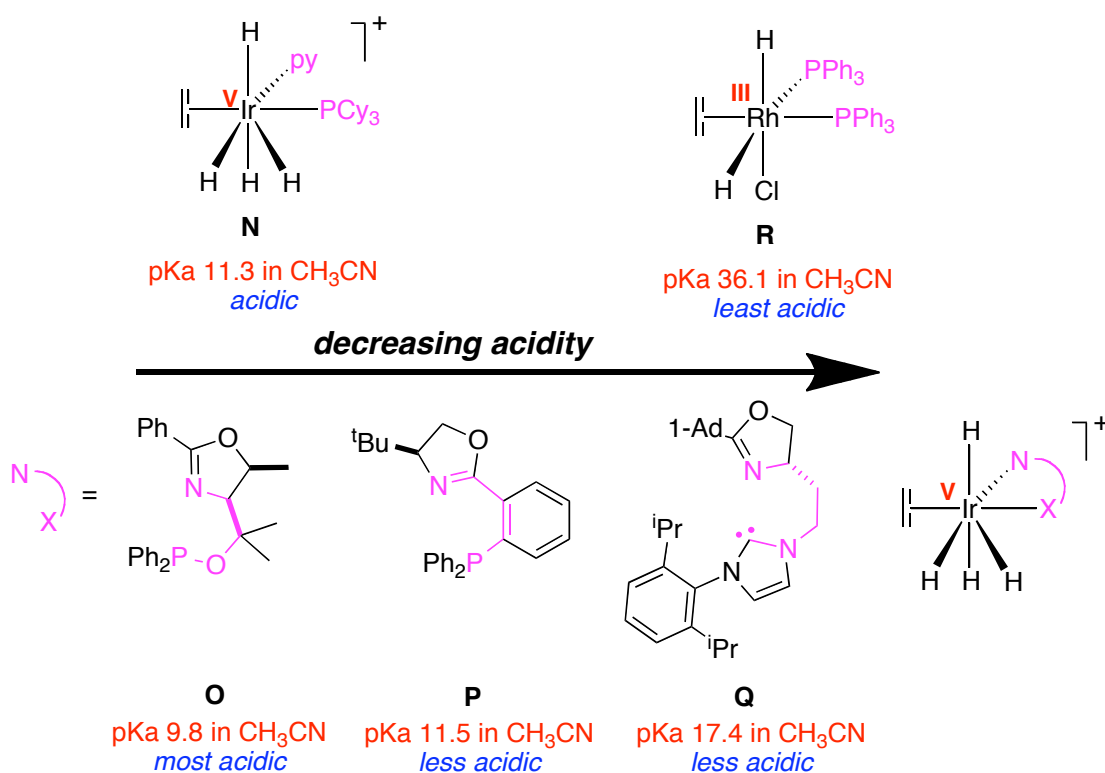
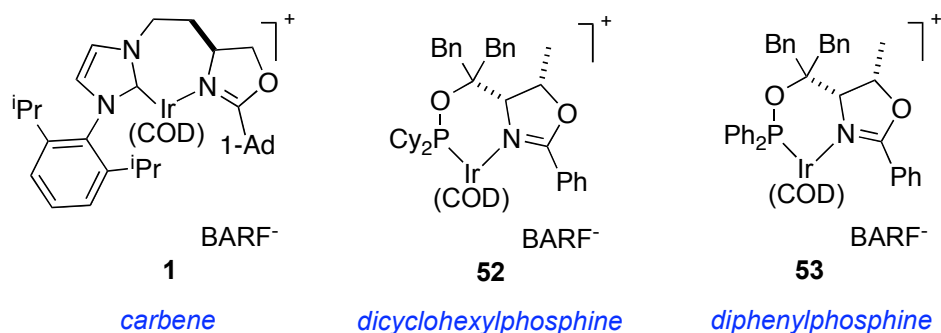


Figure 4.5. Relative acidities of putative intermediates in hydrogenations.

4.3.3. Experimental evidences for the acidity difference



It was a study on enol ether substrates that originally led us to suspect that more protons were produced when *N,P*-Ir-catalyst precursors were used relative the corresponding carbene catalyst. Specifically, Andersson *et al* had noted^{45,46} that alkyl enol ethers gave *complex mixtures* when hydrogenated using one of their *N,P*-iridium catalysts, but we observed the same reaction gave only the expected hydrogenation products when our *N,carbene*-iridium catalyst **1** was used.⁴⁷

In the present work we expanded the scope of our studies to include catalyst precursors **1**, **52** and **53** in hydrogenation of the acid-sensitive enol ether **I**. We predicted these catalyst precursors would give progressively more acidic intermediates in hydrogenations. This assertion was based on the assumption that the carbene ligand is a better σ -donor than either of the *P*-ligands and, of those, the PCy₂ system has superior σ -donating properties.^{148,151-153} The degree of backbonding to these ligands is likely to be minor, and to follow the opposite trend.¹⁵⁴⁻¹⁵⁶ Figure 4.6 shows ¹H NMR spectra of crude materials isolated from these reactions. The desired product **54**, and almost nothing else, was formed when the carbene complex **1** was used. The dicyclohexylphosphinite complex **52** gave much less of the desired ether product **54** and relatively more byproducts. At the other extreme, the diphenylphosphinite complex **53** gave less than 5% of **54** (*ie* almost none by NMR), and mostly undesired impurities.

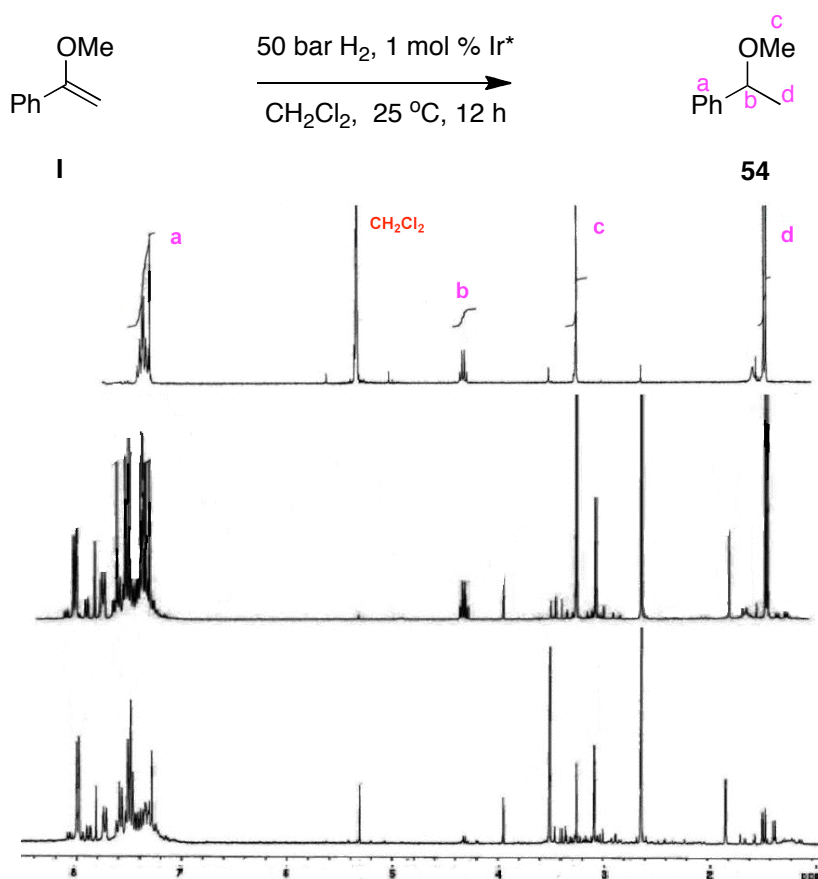
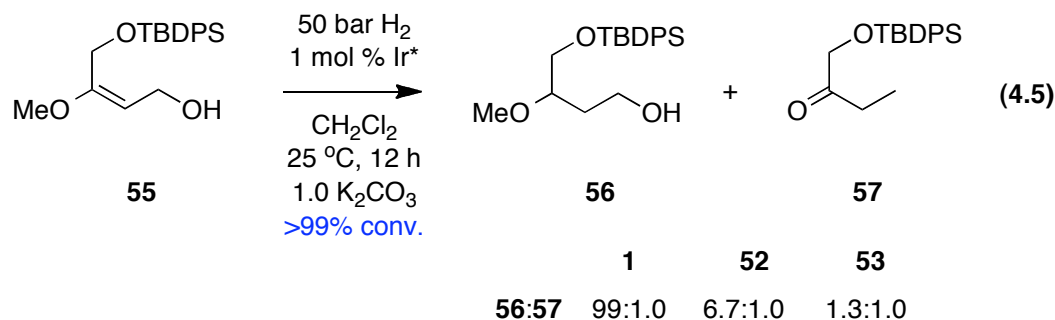


Figure 4.6. Hydrogenation of the acid sensitive enol ether **I** with complexes **1**, **52**, **53** give progressively less of the anticipated ether product **54**.

The byproducts shown in Figure 4.6 could not be conveniently isolated and characterized. However, hydrogenation of the enol ether **55** gives mainly two products: **56**, from direct addition of hydrogen, and **57** via acid-mediated rearrangement and hydrogenation.⁴⁷ This reaction only gave the direct hydrogenation product **56** if a base, *eg* K₂CO₃, was added.⁴⁷ Complete conversion and almost quantitative yields were achieved using all the three catalyst precursors **1**, **52** and **53** in these reactions. Product ratios obtained (¹H NMR) when **55** was hydrogenated using catalysts **1**, **52** and **53** are shown below (reaction 4.5). More of the acid-derived byproduct **57** was formed from the dicyclohexylphosphinite complex **52** than from the carbene, and most accumulated when the diphenylphosphinite complex **53** was used as the catalyst precursor. Thus the

amount of direct hydrogenation product follows the order **1** > **52** > **53**, *ie* the amount of **56** decreases as the anticipated acidities of the predicted intermediates increase.



A second set of evidence for the acidity effects comes from deuterium labeling studies. Several years ago we observed addition of deuterium to alkenes gave some label incorporation at sites other than those corresponding to direct addition.²³ In the light of the data presented above, we postulated that abnormal *D*-incorporation arises via addition of D^+ to the alkene, loss of H^+ to give isomerism, then addition of D_2 (Scheme 4.3). Table 4.6 shows experiments designed to test this hypothesis by using complexes **1** and **53**. According to this hypothesis, **53** should generate more protons in the hydrogenation reactions and give more “abnormal” deuteration. Comparing entries 1 with 2, and 4 with 5, for substrate **58** indicates levels of abnormal deuterium incorporation (*in red*) were *greater* without K_2CO_3 (indicating acidic conditions favor abnormal *D*-incorporation), and that the *N*,*carbene*-catalyst **1** (entries 1 and 2) gave significantly *less* abnormal incorporation than the *N,P*-catalyst **53** (entries 4 and 5). This is consistent with less generation of acid from the hydrogenation reactions involving the carbene **1** relative to the *N,P*-complex **53**.

Scheme 4.3. Rationale for the deuterium scrambling.

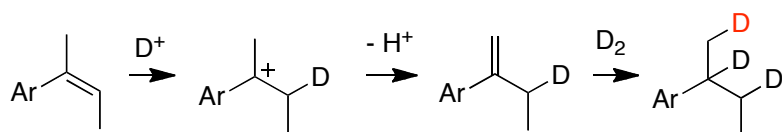
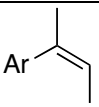
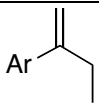
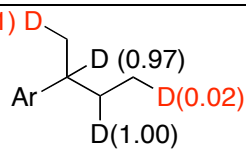
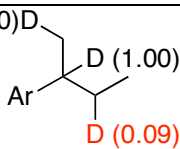
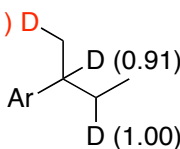
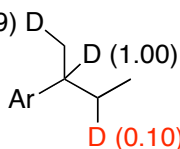
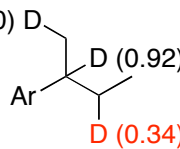
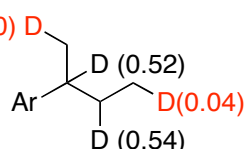
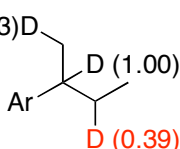
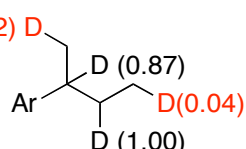
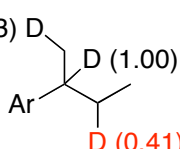
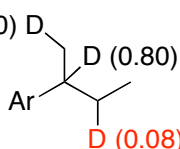
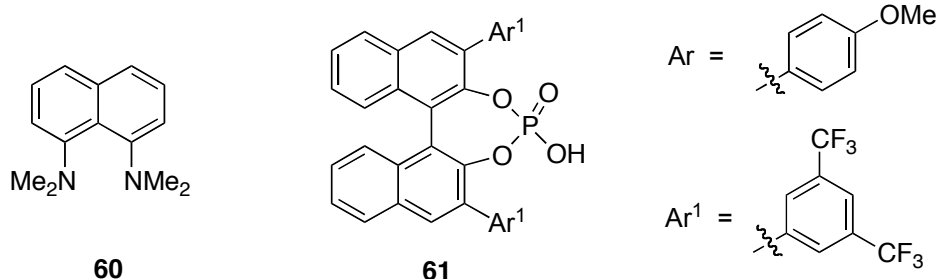


Table 4.6. Deuteration of styrene derivatives.^a

		alkene $\xrightarrow[\text{CH}_2\text{Cl}_2, 25\text{ }^\circ\text{C}, 20\text{ h}]{20\text{ bar D}_2, 1\text{ mol } \% \text{ Ir}^*}$ alkane	
catalyst/additive		 58	 59
1	1/ none		
2	1/ 1.0 eq K ₂ CO ₃		
3	1/ 0.015 eq 61	-	
4	53 / none		
5	53 / 1.0 eq K ₂ CO ₃		
6	3 / 0.5 eq 60	-	

^a Relative to the maximum, 1.00, with the results of indirect addition shown in red, determined by ²H NMR of the crude deuteration products.



The same trends observed for deuteration of substrate **58** were seen for **59** except that addition of K_2CO_3 did not significantly change the levels of abnormal deuterium incorporation. However, the levels *were* decreased when a stronger base, proton sponge **60**, was added to the deuteration mediated by catalyst **53** (compare entry 4 – 6). Conversely, when the acid **61** was added instead, the levels of abnormal deuteration *increased* (compare entry 1 - 3).

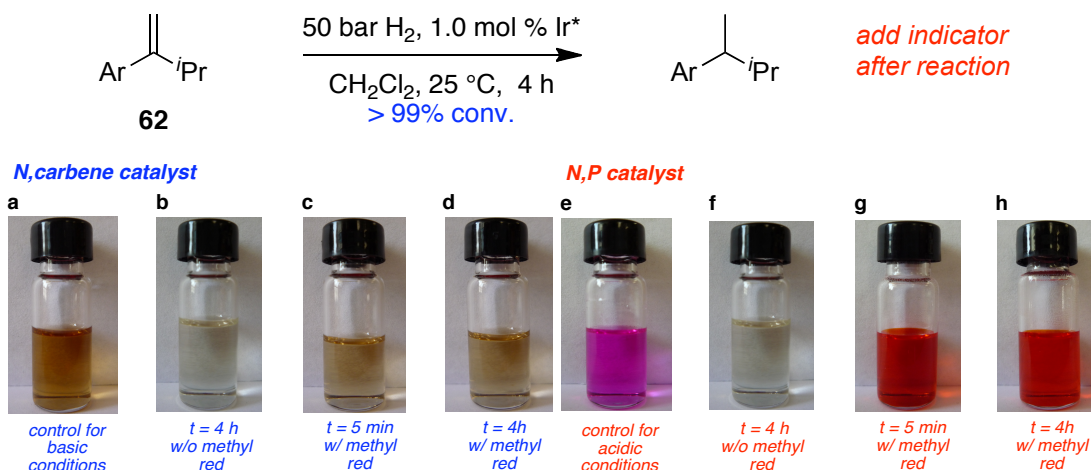


Figure 4.7. Hydrogenation with catalyst **1**: **a** methyl red with Et_3N in CH_2Cl_2 (control for base); **b** without indicator (after 4 h); **c** with methyl red added after 5 min; and, **d** with methyl red added after 4 h. Hydrogenation with catalyst **53**: **e** methyl red with acid **61** in CH_2Cl_2 (control for acid); **f** without indicator (after 4 h); **g** with methyl red added after 5 min; and, **h** with methyl red added after 4 h.

Perhaps the most dramatic illustration of pH in the hydrogenation reactions came from simple experiments using substrate **62** and the acid-base indicator “methyl red”

(orange under basic conditions, and red in acid) (Figure 4.7). Methyl red was added: (i) 5 min after the hydrogenation reaction began; and, to another sample, (ii) *after* the reaction was completed (4 h). Control experiments demonstrate methyl red gives a red coloration under acidic conditions in this environment (frame e). Hydrogenation using the carbene catalyst **1** (frames c and d) and the *N,P*-system **53** (frames g and h) show the latter is clearly more acidic. Frames c and g suggest acidic intermediates formed after only 5 min in the reaction.

We suspect that proton concentrations in hydrogenation reactions are particularly important for tetrasubstituted alkenes substrates like **63**.¹⁵⁷ High levels of abnormal deuteration were observed for the catalyst precursors that are most likely to generate acid, *ie* **52** and **53** (Figure 4.8). Further, carbene **1** did not hydrogenate these same tetrasubstituted alkenes. This could be because of steric factors. However, if acid was generated and the alkene isomerized to a 1,1-disubstituted form then complex **1** should reduce this material. Consequently, it is possible that the carbene complex **1** simply generates *less* acid than **52** and **53**, hence the reaction does not proceed in the former case.

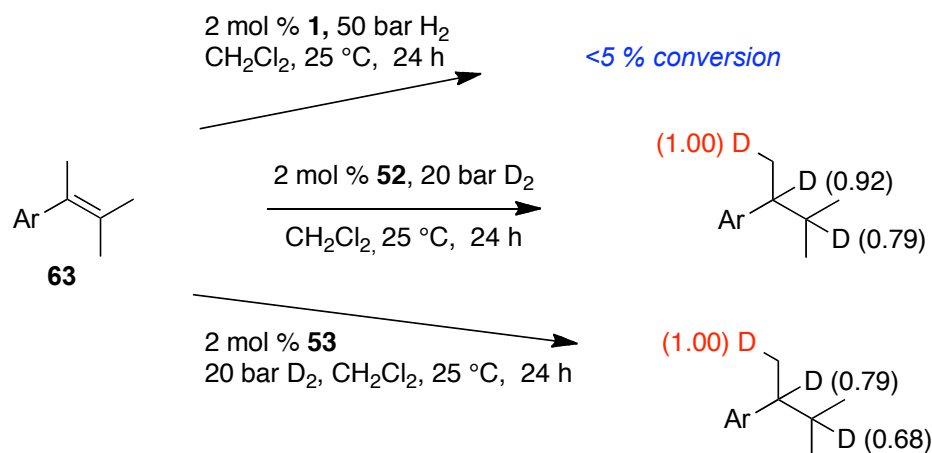
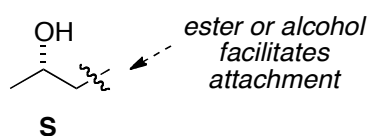


Figure 4.8. Abnormal deuterium distributions for the tetrasubstituted alkene **63** were *less* for the catalyst precursor **52** than with **53** whereas minimal conversion was obtained when the carbene **1** was used.

4.4 Conclusions

The data presented here demonstrated that our Ir-*N*,carbene catalyst **1** is a highly efficient catalyst for the enantioselective hydrogenation of simple unfunctionalized alkyl vinyl ethers. Hydrogenation of substrates **47** and **48** both provide access to the terminal fragment **S** in more complex molecules. That small motif is common in natural products and their analogs; consequently, hydrogenation of these substrates, particularly **48**, can be regarded as a route to this privileged chiron.



The data presented here also shows that hydrogenations of alkenes using chiral analogs of Crabtree's catalyst can be sensitive to protons generated by the catalytic intermediates. Further, the carbene catalyst precursor **1** is *less* inclined to generate protons than the *N,P*-systems **52** and **53** (in that order). We also have shown that the acidities of catalytic intermediates in hydrogenation reactions may impact the product distributions for acid-sensitive substrates, like enol ethers. For some other alkenes, acid-mediated isomerization might compete with direct addition of hydrogen in ways that is not apparent until deuterium labeling is used. Asymmetric hydrogenations of tetrasubstituted alkenes, for instance, are especially vulnerable to this complication because the direct addition of hydrogen is relatively slow due to steric effects, while protonations are fast because they give carbocations that are both benzylic and trisubstituted. It will be interesting to see how acidities of M-H bonds in hydrogenations can impact other acid-sensitive substrates. Acidities of metal hydride intermediates are important in many transition metal catalyzed reactions; in some cases, dramatically altered catalytic behavior on phosphine-to-carbene ligand substitution will be indicative of this.

CHAPTER V

ASYMMETRIC HYDROGENATION APPROACHES TO α -METHYL- γ -ALKYL γ -AMINO ACIDS

5.1 Introduction

γ -Amino acids include some important biologically active compounds in the central nervous system (CNS) of mammals. Over the last few years, significant interest in the stereoselective synthesis of γ -amino acids has been shown. Practical application of linear and cyclic chiral γ -amino in the synthesis of α,β - and β,γ -hybrid peptides acids has also been reported. These clearly demonstrate the theoretical interest and the practical importance of γ -amino acids.¹⁵⁸⁻¹⁶⁵

γ -aminobutyric acid (GABA) **64** is the major inhibitory neurotransmitter in the CNS of mammals. It exerts its physiological action through interaction with three receptor subtypes: termed GABA_A, GABA_B, and GABA_C. The GABA_A and GABA_C receptors are ligand-gated ion channels permeable to anions and convey fast synaptic transmission, whereas GABA_B is a G-protein coupled receptor, which modulates the synaptic transmission through intracellular effector systems.¹⁶⁶

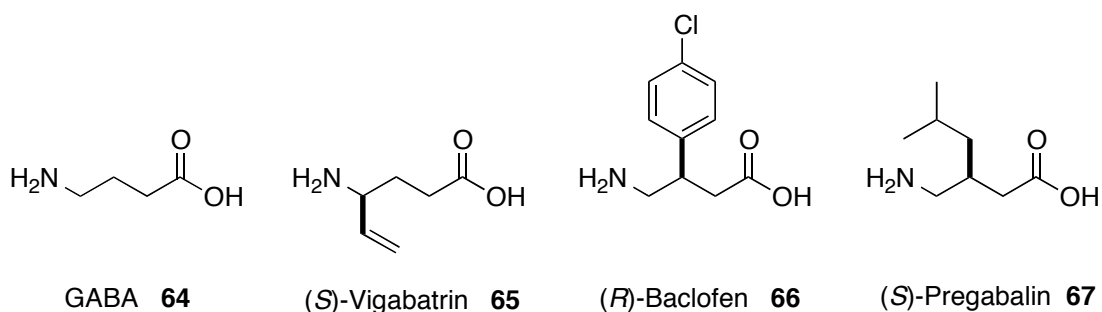
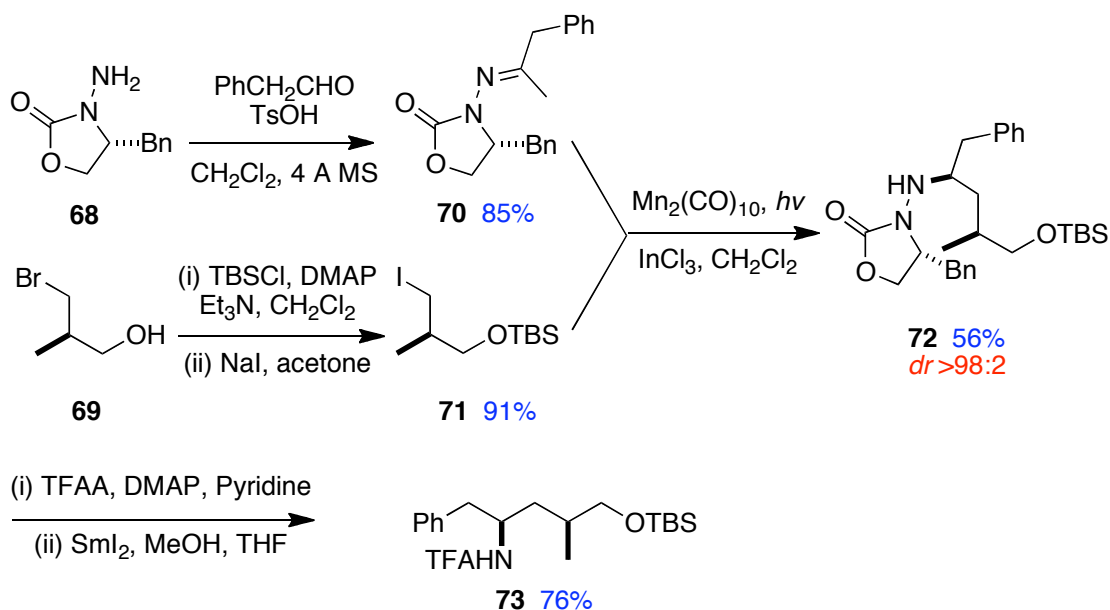


Figure 5.1. Structures of GABA derivatives that are commercialized drugs.

GABA deficiency is associated with several important neurological disorders such as Huntington's and Parkinson's disease, epilepsy, and other psychiatric disorders, such as anxiety and pain. However, oral or intravenous administration of GABA is inefficient due to its low lipophilicity, and its poor ability to cross the blood–brain

barrier (BBB). Consequently, the synthesis of more lipophilic GABA derivatives that have better permeability to the BBB is an area of interest. Such considerations had also led to pharmaceutical compounds (Figure 5.1).

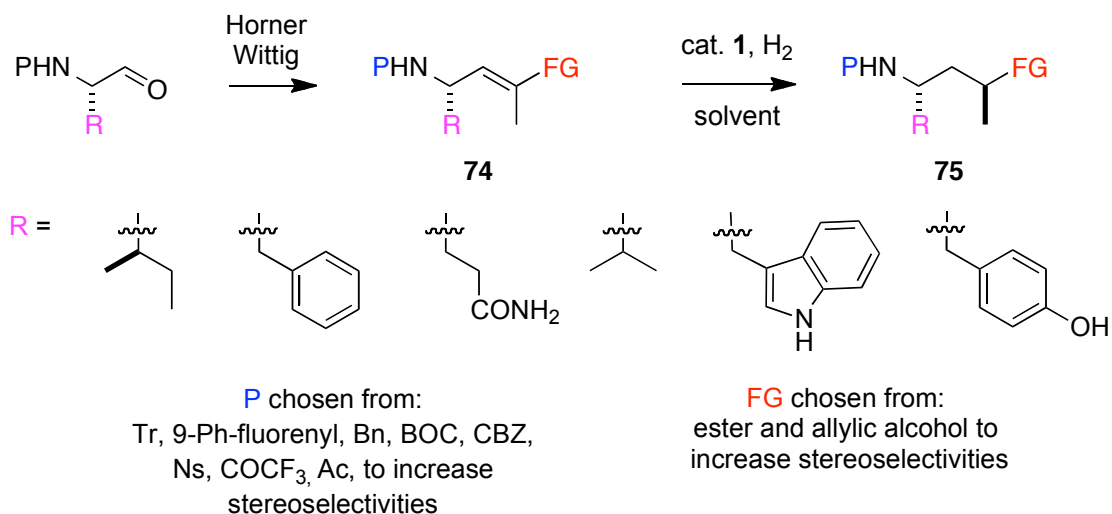
Scheme 5.1. Mn-mediated addition of functionalized iodide to hydrazone.



In contrast to α - and β -amino acids, general synthetic methods to supply γ -amino acids are comparatively underdeveloped.^{167,168} Previous strategies for synthesis of α -methyl- γ -alkyl- γ -amino acids have exploited Pd/C catalyzed hydrogenations,^{169,170} alkylation of enolates of N -substituted γ -amino acids¹⁷¹ or pyrrolidinones,¹⁷² regioselective N -tosylaziridine opening,¹⁷³ asymmetric aldol reaction followed by removal of the secondary hydroxy group,¹⁷⁴ and zirconium catalyzed diastereoselective intramolecular ester transfer reaction of N -alkenylcarbamate derivatives.¹⁷⁵ Most of these methods provided the desired products with low stereoselectivities. Also these reactions were not very practical in terms of the availability of the starting materials, the reaction yields and the difficulty of separation of the desired diastereoisomer from the product mixture. To the best of our knowledge, the most general methods to date for preparing the α -methyl- γ -alkyl γ -amino acids were reported by Friestad, which used the

Mn-mediated coupling of functionalized iodides and hydrazones (Scheme 5.1).^{176,177} Since both enantiomers of *N*-amionoxazolidione **68** are commercially available, and also both enantiomers of alkyl bromide **69** are conveniently available, so all the four diastereoisomers can be obtained via this route. More importantly, both the α -substituents and the γ -substitutents can be easily modified using different aldehydes and bromoalcohols in this reaction. The only drawback for this methodology is that the reaction involves the use of excess Mn and In metals; this is undesired for pharmaceutical industries.

Scheme 5.2. An asymmetric hydrogenation route to α -methyl- γ -alkyl amino acids.



Inspired by successful syntheses of 1,3-dimethyl chirons and 1,3-hydroxymethyl chirons, we realized new ground could be broken not only by being able to synthesize this important chirons via our iridium catalyzed asymmetric hydrogenations but also being able to incorporate pharmacologically active side-chains (not just Me, Et, *etc*). Stereoselectivities in reductions of substrates **74** could derive from the catalyst, and from the substrate. Largely inconsequential groups like the protecting groups **P** and **FG** can be varied to increase “substrate vectors” to enhance stereoselectivities in the desired direction (Scheme 5.2; both hands of the catalyst are available).

The hydrogenated products have somewhat more conformational constraints than compounds like GABA, Preggabaline and Vigabatrin because of the presence of the methyl group; this is useful because stereochemistries can then be varied to access preferred binding conformations. Amino acid derived side chains **R** will be selected from those presented above. An *iso*-leucine side chain is desirable because the chiral center in this provides an indicator for racemization at any stage in the procedure. The phenylalanine, glutamine, and valine side-chains are found in some pharmaceutically active α -alkyl- γ -alkyl- γ -amino acids that we have found in the literature (Figure 5.2). Side chains from tryptophan and tyrosine are included because these are two of the most common side-chains found at “hot-spots” for protein-protein interactions and are known to be interesting pharmacophores.¹⁷⁸

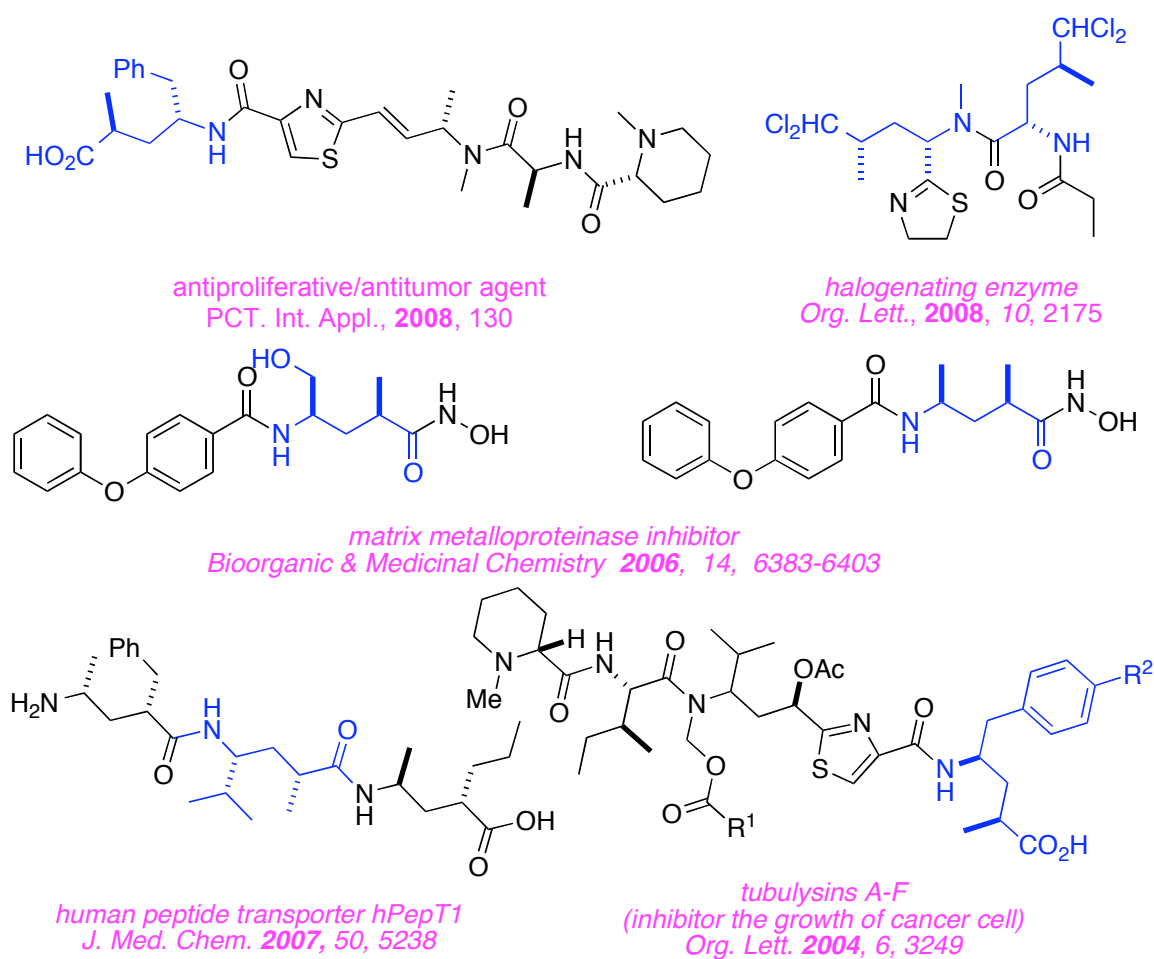


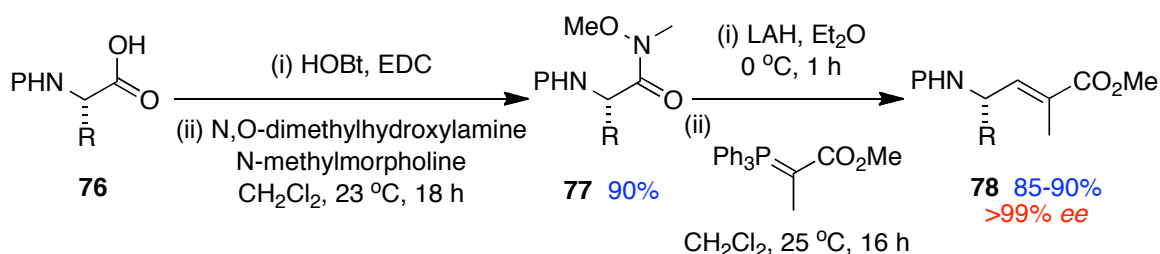
Figure 5.2. Examples of pharmaceutically active α -methyl- γ -alkyl- γ -amino acids.

5.2 Results and discussions

5.2.1 Hydrogenation studies

Dr. Amber Schaefer, who is a postdoc researcher in our group, initiated this research project. Starting from various protected amino acids **76**, Weinreb amides **77** can be obtained with high yields in one step.¹⁷⁹ The amides **77** was reduced to aldehyde with LAH at 0 °C, and without purification the aldehydes were directly converted to the alkenes **78** under the standard Wittig conditions. Thus enantiomeric pure allylic amines **78** can be obtained in three steps with high yields (Scheme 5.3).

Scheme 5.3. Synthesis of chiral allylic amines.



With these alkene substrates in hand, Dr. Schaefer tried several hydrogenation reactions with our Ir-*N,carbene* catalyst **1**, and the results are shown in Figure 5.3. As can be seen here, four amino acids with different side chains and four different protecting groups for the amine have been used. However, none of these alkene substrates gave satisfactory results and the diastereoselectivities for these reactions are poor.

Even though the preliminary results from Dr. Schaefer did not show good diastereoselectivities in the hydrogenation reactions, some lessons can be learned from those studies. First, most of the substrates she tried can be hydrogenated well with catalyst **1**. The protected amine will not poison the catalyst. Second, all the substrates that have been tried are α,β -unsaturated esters. It occurred to us that this type of alkenes might not be suited to hydrogenation in terms of diastereoselectivity. Last, Dr. Schaefer had tried several different alkene substrates with four different side chains. She found

the stereoselectivities for those substrates were similar. My role in this project was to identify a suitable substrate class for both *syn*- and *anti*-diastereoisomers.

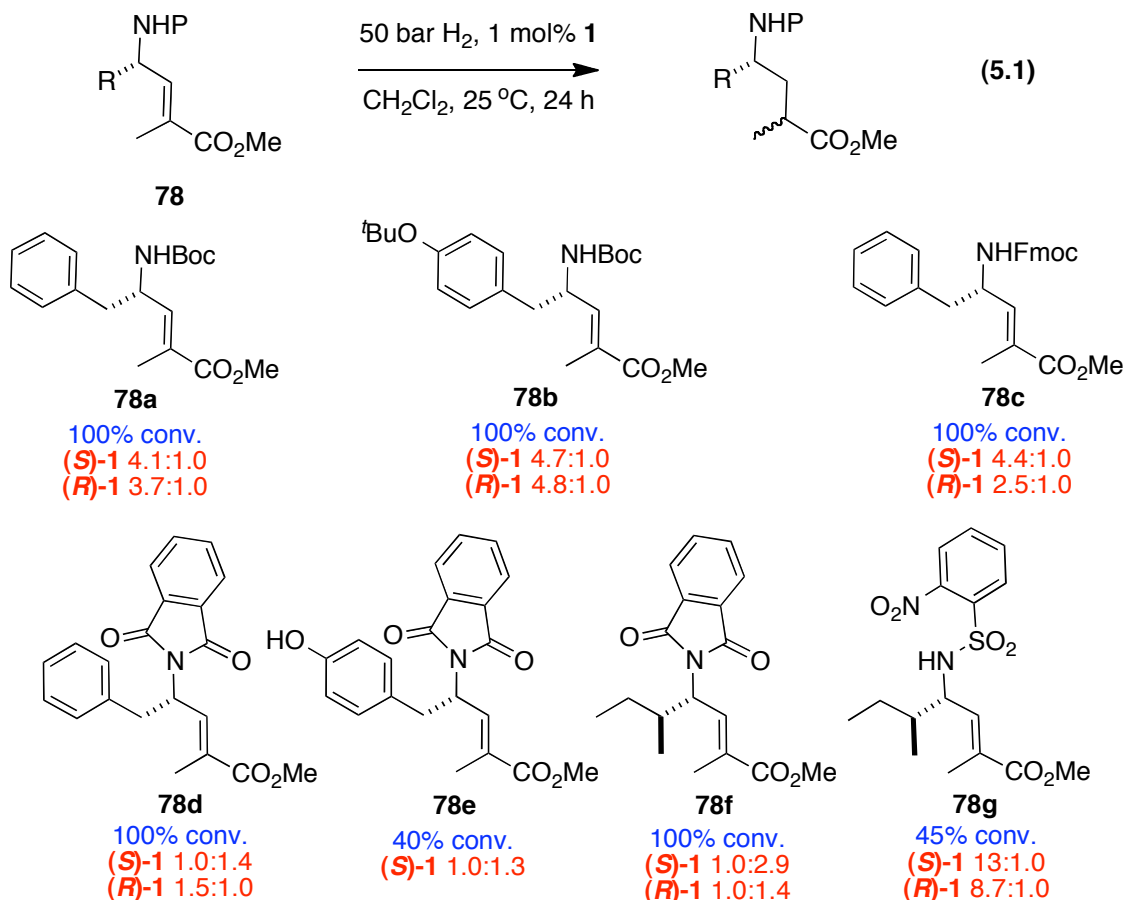
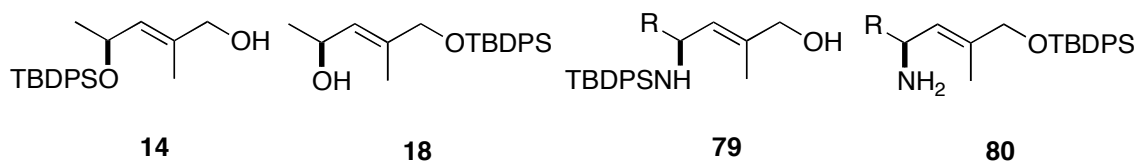


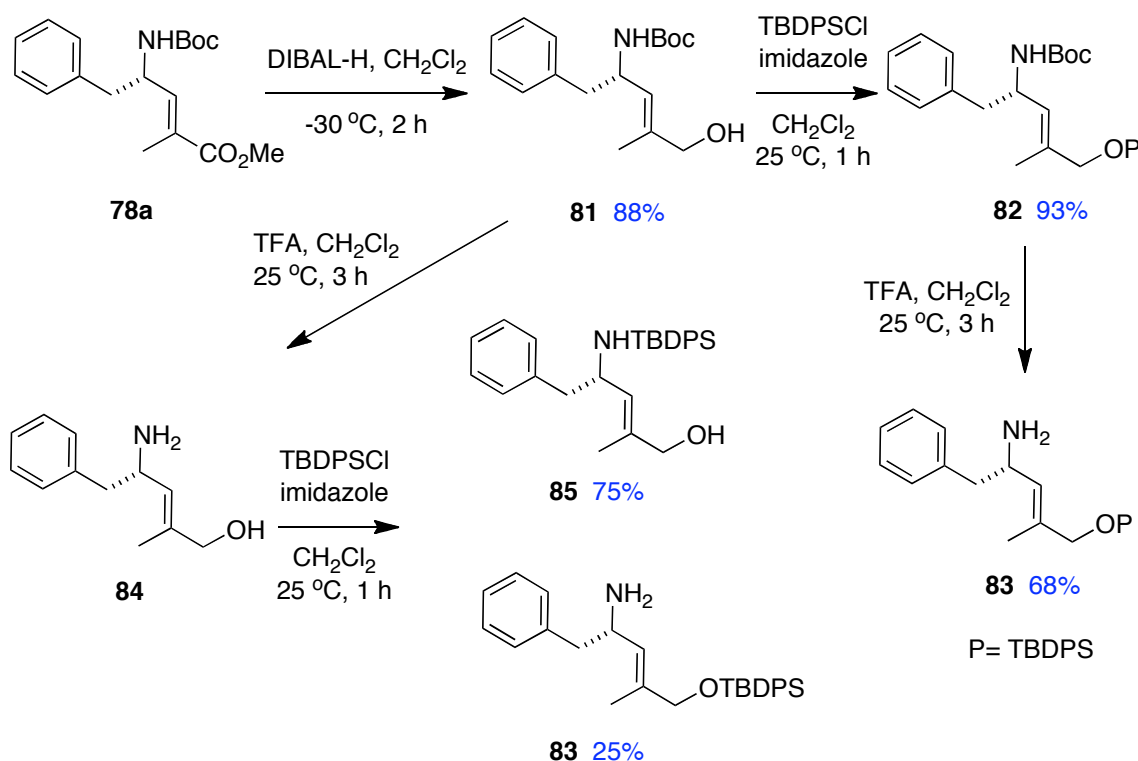
Figure 5.3. Preliminary results for the hydrogenation of chiral allylic amines.

Our 1,3-hydroxymethyl chirons synthesis project found that good diastereoselectivities for *syn* and *anti* terminal isomers can be achieved in the hydrogenation of substrates **14** and **18**. Allylic amines **79** and **80** are structurally similar, so we hypothesized they might provide better stereoselectivities than those substrates tried by Dr. Schaefer.



Starting from alkene **78a**, the DIBAL reduction afforded the allylic alcohol **81** with 88% yield. Protecting the hydroxy group with TBDPSCI and removing the Boc protecting group afforded alkene **82** and **83**. Starting from the same intermediate **81**, the amino alcohol **84** can be synthesized. Without further purification, **84** was treated with 1.1 eq. TBDPSCI and after 1 h a mixture of two different allylic amines were obtained. Interestingly, the amino protected product **85** was the major product (Scheme 5.4).

Scheme 5.4. Syntheses of modified chiral allylic amines.



With these allylic amines in hand, a series of hydrogenations were undertaken. Changing the functional group from ester to allylic alcohol did not improve the diastereoselectivity dramatically (compare **78a** to **81**, Figure 5.4). However, protecting the free hydroxy group of **81** with a bulky TBDPS protecting group significantly improved the diastereoselectivity when the (*S*)-**1** was used (alkene **82**). The alkene **83**,

which originally was thought to give a good diastereoselectivity for the *anti*-isomer, was not hydrogenated at all under the general hydrogenation conditions. Adding base did not improve the conversion. This is not very surprising because the strong coordinating ability of the free amine might kill the catalyst during the catalytic cycles. On the contrary, the alkene **85**, which was thought to be a good substrate for the *syn*-isomer, did provide an excellent diastereoselectivity when the (*S*)-**1** was used (dr >19:1.0). However, the highest conversion was only 60% when 1 mol% catalyst was used. Elevated hydrogen pressure (100 bar) and reaction temperature (60 °C) did not improve the conversion. When 5 mol% of (*S*)-**1** was used, 100% conversion was obtained and the stereoselectivity was still very good (dr >19:1.0) (Figure 5.4).

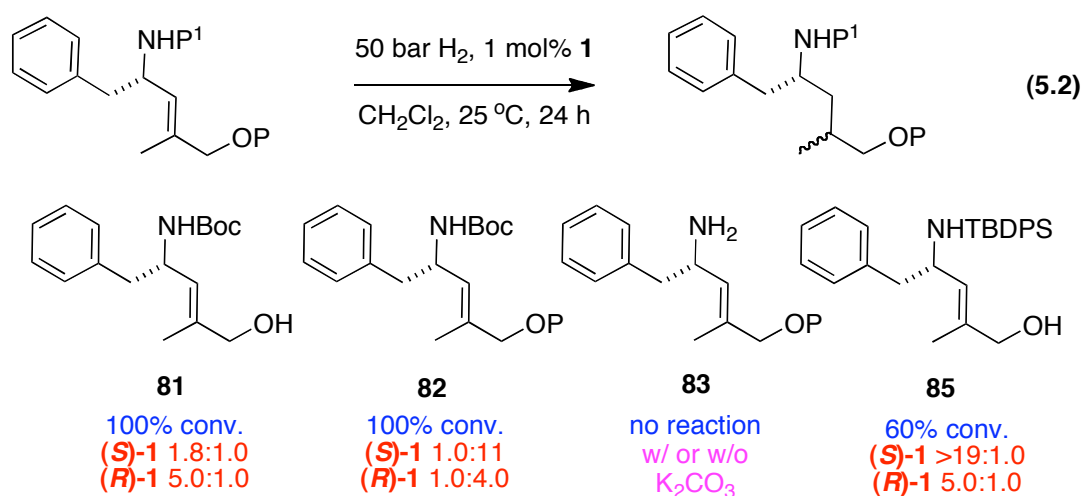
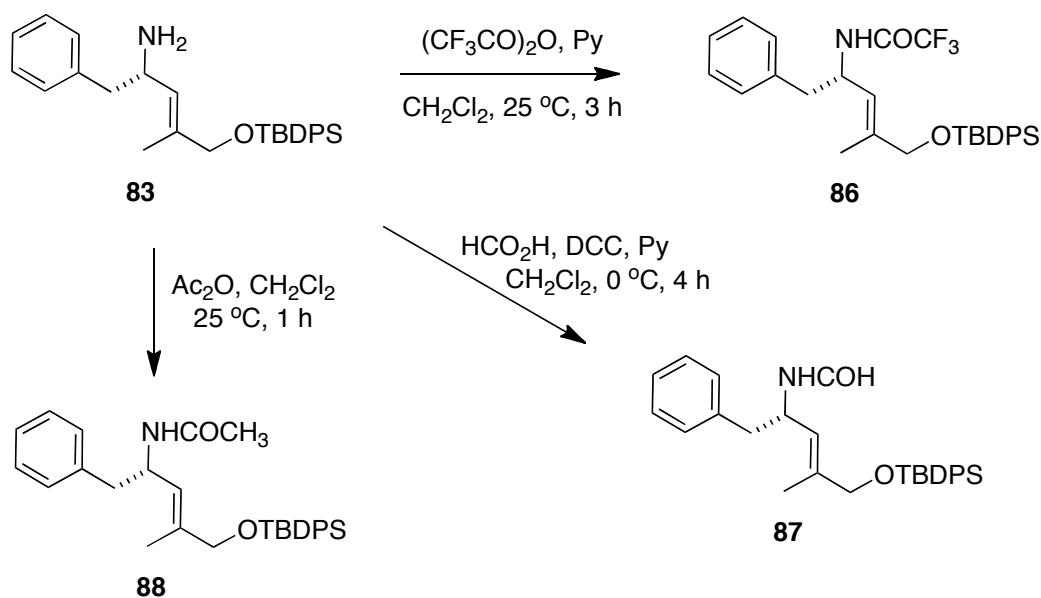


Figure 5.4. Hydrogenation results for the first cycle of modified chiral allylic amines.

Considering the diastereoselectivity improvement from **81** to **82**, we realized that a bulky hydroxy protecting group would be beneficial for the reaction. Thus we did not change anything about this part in subsequent substrate structure modifications. Based on the Rh catalyzed hydrogenation of enamide reactions, we thought the carbonyl from the Boc protecting group might be a directing functional group for the hydrogenations. However, the bulky *tert*-butyl group possibly would hamper this coordination. As a

consequence, we became interested in smaller protecting groups than Boc that also has a coordinating carbonyl group, *e.g.* $\text{CF}_3\text{CO-}$, $\text{CH}_3\text{CO-}$, HCO- (Scheme 5.5).

Scheme 5.5. Syntheses of modified chiral allylic amines **86-88**.



The hydrogenation results of the newly synthesized alkene substrates supported our hypothesis. Hydrogenation of alkene **86** provided an excellent stereoselectivity when (*S*)-**1** was used, although 4 mol% catalyst was needed for 100% conversion. When the amine-protecting group was changed to $\text{CH}_3\text{CO-}$ (alkene **88**), high diastereoselectivity was obtained and catalyst loading was also reduced to 2 mol%. For the alkene **87**, the stereoselectivity was not very good for both enantiomers of the catalyst. Since the alkene **87** was a mixture of the amide rotamers, it is not very surprising that the diastereoselectivity was moderate (Figure 5.5).

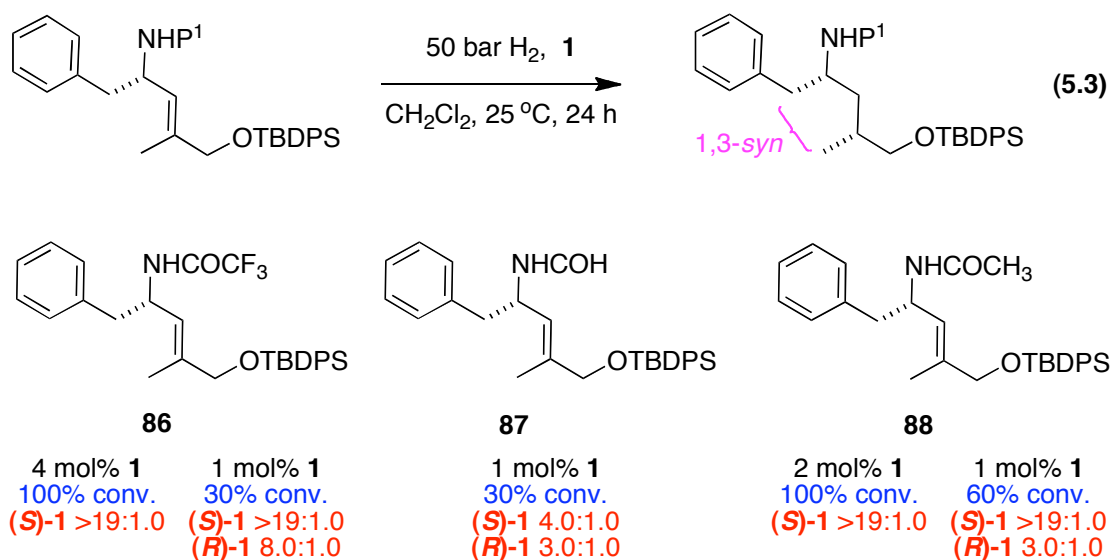
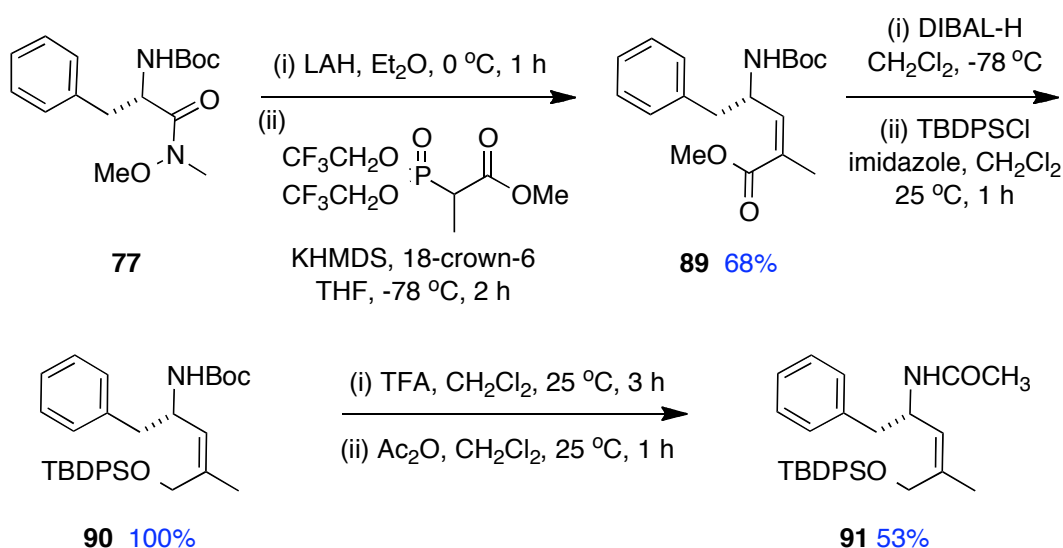


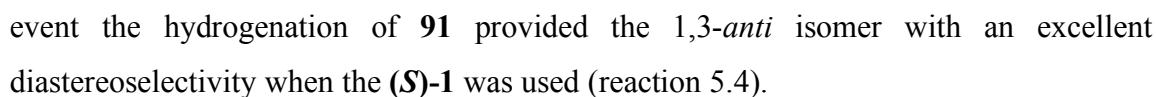
Figure 5.5. Hydrogenation results for the second cycle of modified chiral allylic amines.

Despite all kinds of efforts, all the previous hydrogenations afforded the 1,3-*syn* isomers as the major isomer for the α -methyl- γ -alkyl- γ -amino acids. However, our previous experience for the hydrogenation reactions indicated the 1,3-*anti* isomers might

Scheme 5.6. Syntheses of Z-chiral allylic amines.



accessible by changing the geometry of the alkenes. Thus starting from intermediate **77**, the Z-allylic amine **91** was synthesized in 6 steps with a 36% yield (Scheme 5.6). In the



5.3 Conclusions

In summary, we have developed a new entry to α -methyl- γ -alkyl γ -amino acids via iridium catalyzed asymmetric hydrogenation of chiral allylic amines. Both *anti*- and *syn*-isomers can be obtained with high diastereoisomeric purities. The study shown here only demonstrated the development progress for the successful production of the allylic amines from phenylalanine. However, based on these studies, other allylic amines that have different side chains should also be suitable substrates for the hydrogenations. Considering the importance the γ -amino acids, we are looking forward to seeing some applications of this stereoselective and environmentally benign method.

CHAPTER VI

HIGHLY DIASTEREOSELECTIVE ROUTES TO α -METHYL- β -HYDROXYL- γ -METHYL CHIRONS VIA IRIIDIUM CATALYZED ASYMMETRIC HYDROGENATIONS

6.1 Introduction

The stereochemical complexity of polyketides presents formidable challenges for organic chemists.¹⁸¹⁻¹⁸³ After the epochal total synthesis of erythromycin A (Figure 6.1) by Woodward, this inherent complexity has captured the imagination of synthetic chemists and the concise assembly of such complex system has been a key driver for the

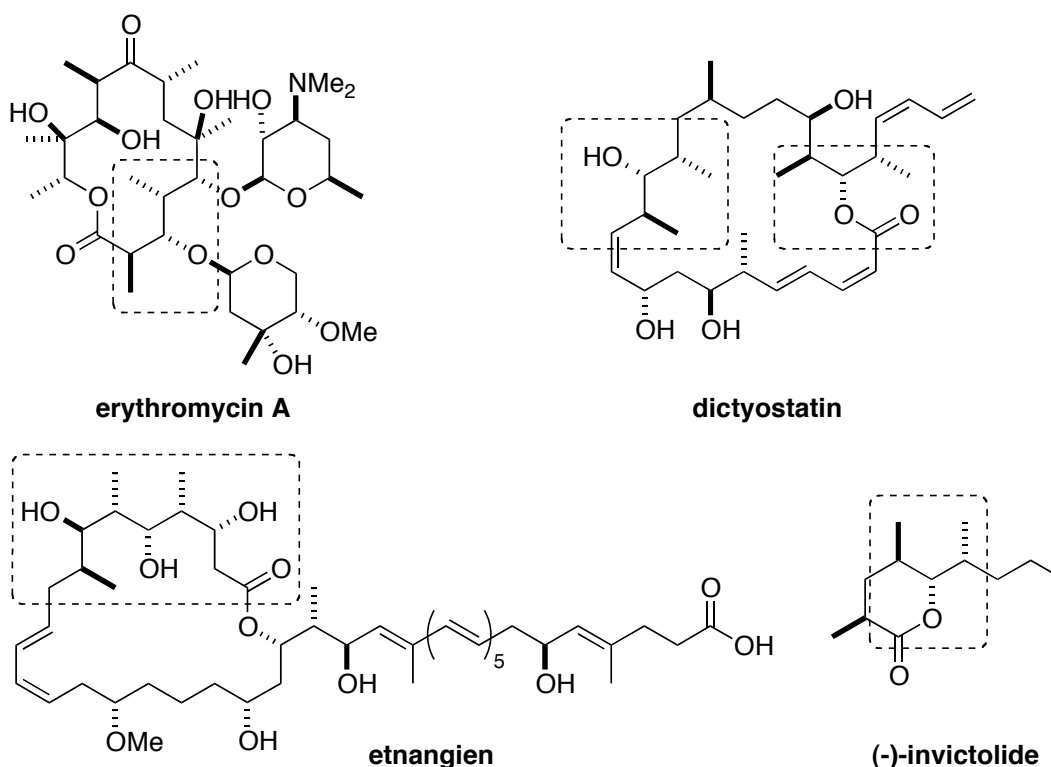
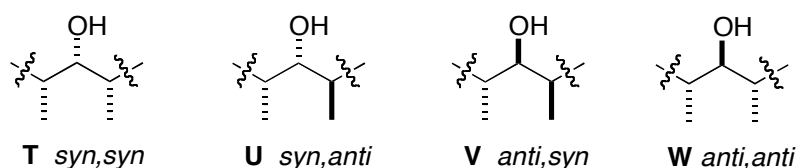


Figure 6.1. Polypropionate fragments in polyketide natural products.

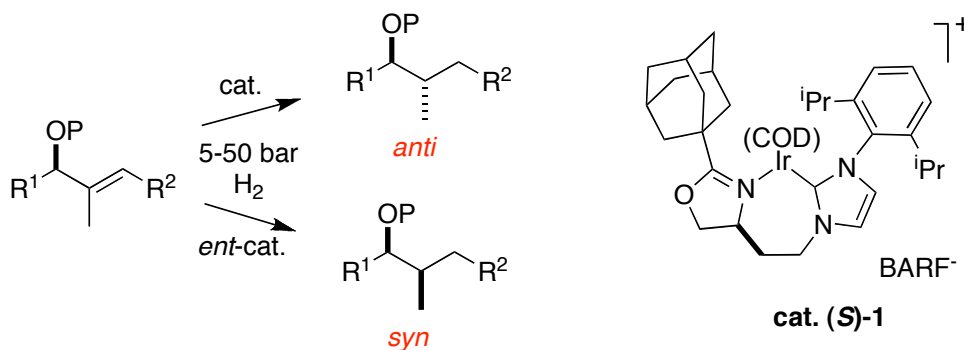
development of new methodologies. A key structural feature in erythromycin A and polyketides in general, such as the macrolide antibiotics dictyostatin or etnangien, are the polypropionate fragments. They are characterized by sequences of methyl-,

hydroxy-, and methyl- bearing stereogenic centers, enabling large numbers of possible stereochemical permutations. Biosynthetically, these are derived by iterative condensations of propionyl subunits and subsequent reduction of the derived β -keto esters.



Mimicking this biosynthetic pathway, aldol reactions between enolates derived from ethyl ketones and α -methylaldehyde are a conventional method for constructing such stereotriads.¹⁸⁴⁻¹⁸⁸ The reactions of crotylmetal reagents with α -methylaldehyde are an important alternative to aldol reactions and have been successfully used for the same purpose.¹⁸⁹⁻¹⁹² In 1987, R. W. Hoffmann surveyed methodology under development for the synthesis of so-called stereotriads **T-W**.¹⁹³ From that review, it was clear that many methods have been developed for the stereoselective synthesis of triads **T-W**. However, of the four, **W** is the most difficult one to access by that time. Also there has been no single strategy that allows the synthesis of all four triads with equal efficiency and stereoselectivity.

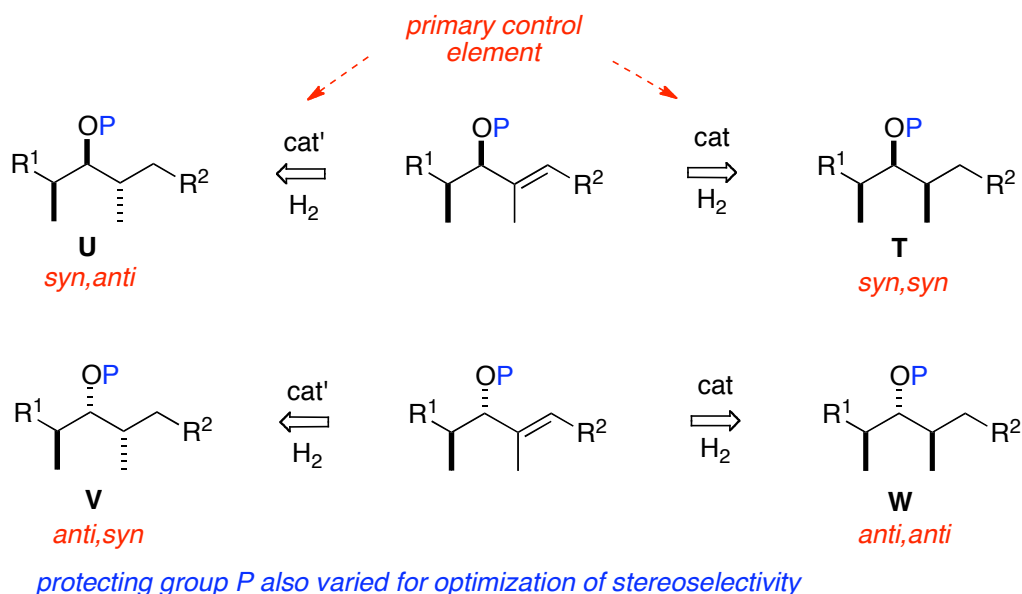
Scheme 6.1. Aldol-type chirons from asymmetric hydrogenations of trisubstituted alkenes.



protecting group P also varied for stereoselectivity optimization

We have previously shown that iridium catalyzed asymmetric hydrogenations can provide aldol-type chiralons with high conversions.⁹⁹ These reactions are catalytic, high stereoselective, and afford both *syn*- and *anti*-aldol products (Scheme 6.1). Looking forward, we are interested in developing hydrogenations of trisubstituted alkenes to access stereochemical triads and higher homologs based on similar strategies. Specifically, starting from a suitable hydrogenation substrates, by choosing the right enantiomer of the catalyst and varying the protecting group on the hydroxy group, a good diastereoselectivity should be able to be obtained. We are very ambitious on this research project and hoping we can obtain all the possible diastereoisomers **T-W** (Scheme 6.2).

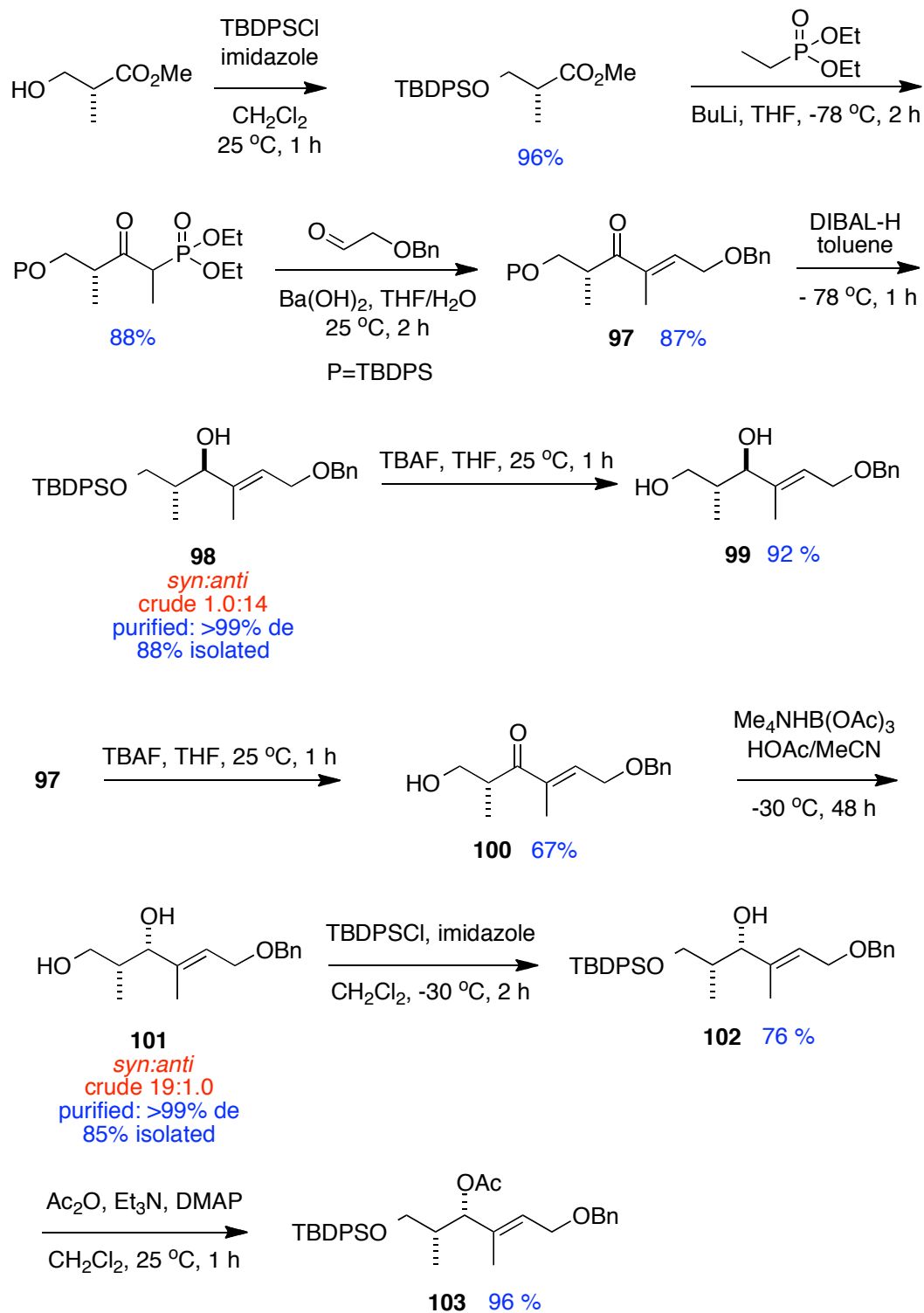
Scheme 6.2. Synthetic plans for the syntheses of stereotriads **T-W**.



6.2 Results and discussions

6.2.1 Syntheses of the hydrogenation substrates

Syntheses of substrates to prepare the stereotriads **T-W** began with *Roche ester*. The key intermediate enone **97** can be made in three steps with high yield. DIBAL-H

Scheme 6.3. Routes to alkene substrates for syntheses of triad **T-W**.

reduction of **97** at -78 °C afforded the key hydrogenation substrate **98** with 88% isolated yield.¹⁹⁴ The newly generated hydroxy group had an *anti* relationship with the pre-existing chiral methyl group. The *syn*- to *anti*-diastereoisomer ratio for the crude product was 14:1.0, which can further increased to >99% *de* after purification with flash chromatography. The preference for the *anti*-isomer in this reduction was presumably due to preferential reduction through a Felkin-Ann transition state.¹⁹⁵ Deprotection of the silyl protecting group with TBAF at 25 °C provided another key hydrogenation substrate **99** with 92% yield (Scheme 6.3).

In contrast, a near exclusive generation of the *syn*-1,2-hydroxy, methyl isomer was observed when the free alcohol **100** was reduced under the reduction conditions exploited by Evans and co-workers.¹⁹⁶ Thus, treatment of **100** with tetramethylammonium triacetoxyborohydride under the tailored reaction conditions that ensure hydroxyl exchange with the triacetoxyborohydride and subsequent intramolecular hydride delivery to the proximal carbonyl provided the desired *syn*-isomer **101** (85%, >19:1.0 *syn:anti*). The diastereoisomer ratio can also be improved via the flash chromatography (>99% *de*). With this intermediate, the alkene **102** and **103** can be easily synthesized via selective functional group protecting (Scheme 6.3).

6.2.2 Syntheses of the stereotriad T-W via asymmetric hydrogenations

Through the iridium catalyzed asymmetric diastereoselective hydrogenations, we were delighted to see that all the four diastereoisomers **T-W** can be obtained with high yields and diastereoisomer purities. Hydrogenation of alkene **98** with (*S*)-**Cat** afforded the most challenging triad **W** with 84% isolated yield. The *syn* to *anti* ratio for the crude product was 1.0:48, which was high enough for other possible homologations. Hydrogenation of alkene **99** with (*R*)-**Cat** afforded another triad **V** with 100% conversion. The *syn* to *anti* ratio for the crude product was 21:1.0. To help to remove the minor *anti*-isomer, the hydrogenation product diol was converted to an acetonide protected ketal, and the resulting triad **V** can be purified easily via flash chromatography, providing the triad **V** with 91% yield and >99% *de* (Figure 6.2).

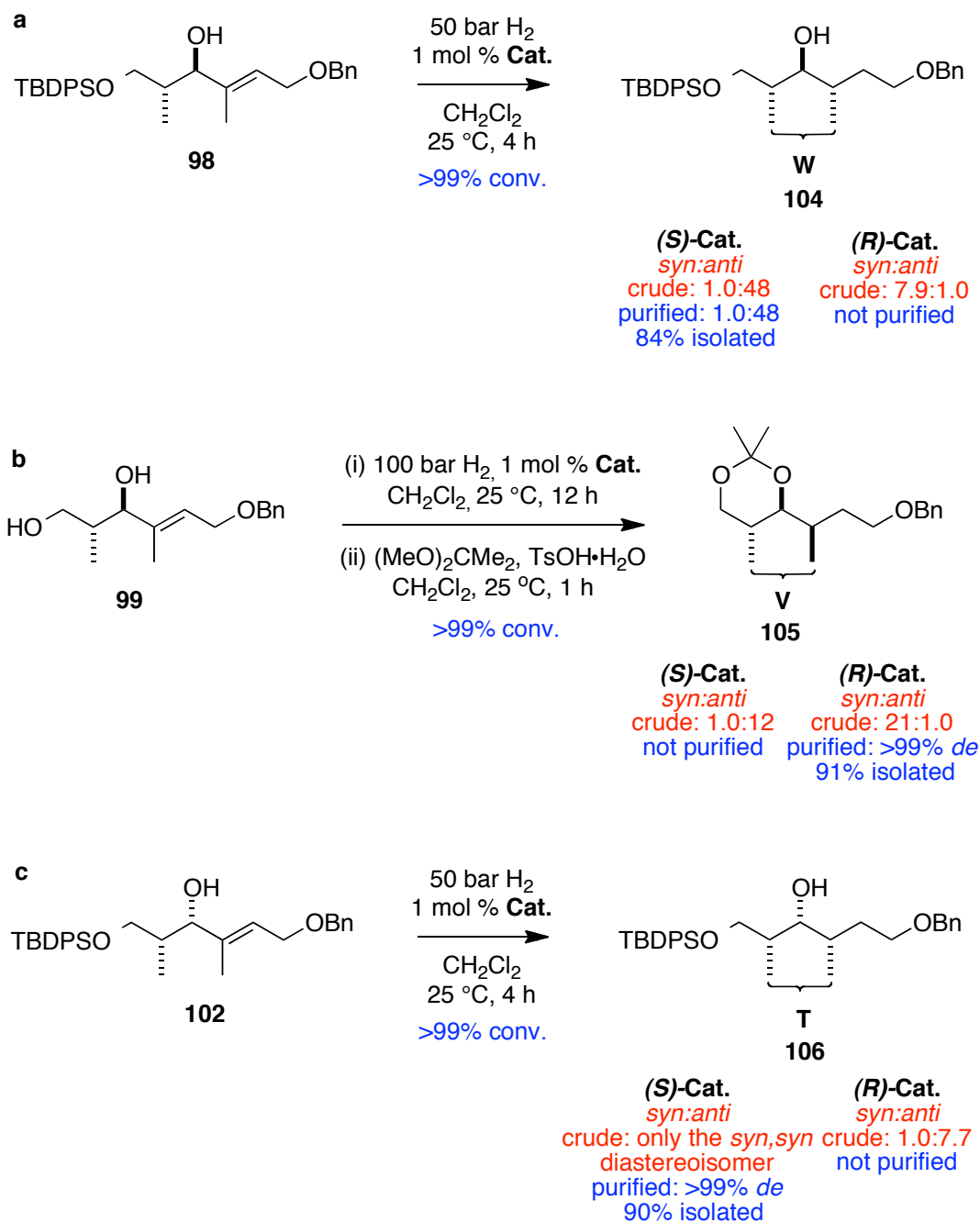


Figure 6.2. Preparation of stereotriad **T-W**. All ratios quoted are from chiral HPLC.

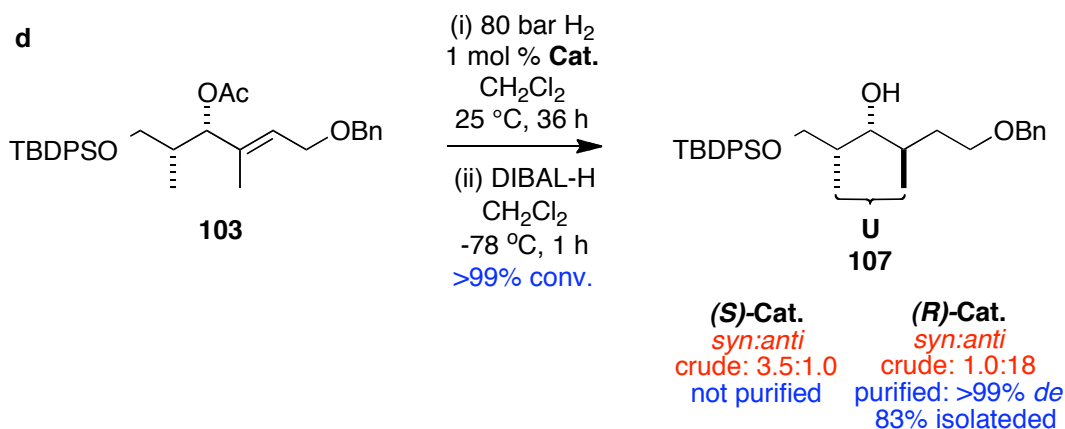


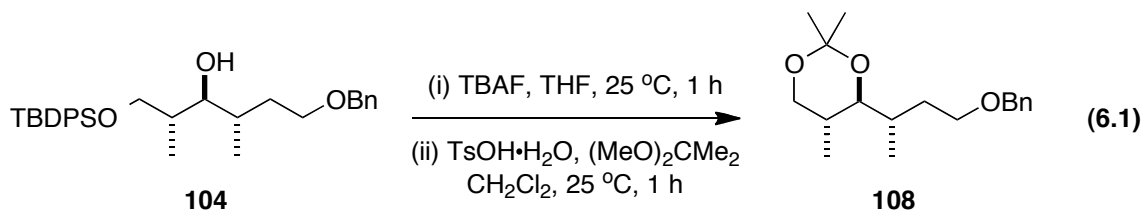
Figure 6.2. Continued.

Very similarly, hydrogenation of alkene **102** with **(S)-Cat** afforded triad **T** with 90% isolated yield. The diastereoselectivity for this reaction was extremely high and only the *syn*-isomer was found in the crude hydrogenation product. Hydrogenation of alkene **103** with **(R)-Cat** afforded triad **U** with 100% conversion. The *syn* to *anti* ratio for the crude product was 1.0:18. To help to remove the minor *syn*-isomer, the hydrogenation product acetate was reduced to an allylic alcohol, and the resulting triad **U** can be purified easily via flash chromatography, providing the triad **U** with 83% yield and >99% *de* (Figure 6.2).

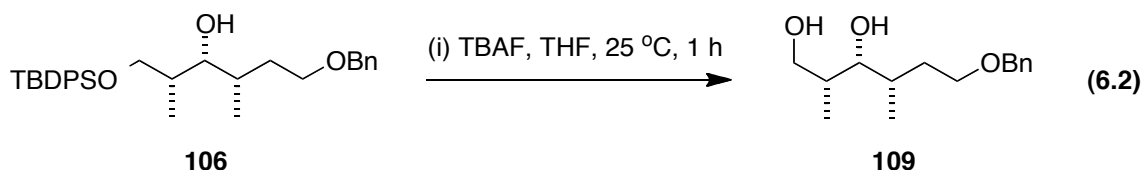
Throughout this study, all the hydrogenation reactions shown here were catalyst controlled, but “substrate vectors” (contributions to the diastereoselectivity by the substrate) were also significant. The data shown here once again demonstrated that our chiral analog of Crabtree’s catalyst is almost uniquely suitable for asymmetric hydrogenation of coordinating unfunctionalized, trisubstituted alkenes. In most cases **Cat** usually can give *catalyst* control for hydrogenations of chiral alkenes. Hydrogenations of these relatively hindered substrates typically would *not* be induced at a significant rate using metal diphosphine complexes. Metal diphosphine complexes only hydrogenate these substrates well if there is a coordinating functional group, in which case substrate control is usually observed.

6.2.3 Relative and absolute configuration determination

All the alkene substrates were made from enantiomer enriched (*R*)-*Roche ester* (98% *ee*). So the absolute stereochemistry was determined by the chirality from the starting material. Hydrogenation of **98** with (*S*)-**Cat** provided the triad **104** with high diastereoselectivity (*syn:anti*, *dr* 1.0:48) (Figure 6.2.a). Starting from **104**, an acetonide derivative **108** can be synthesized in two steps (Reaction 6.1). **108** was a known compound with reported ¹H NMR and ¹³C NMR.¹⁹⁷ Thus **104**, the hydrogenation product of **98**, was determined to be an *anti,anti* stereotriad **W**. Hydrogenation of **99** with (*R*)-**Cat** provided the triad **105** with high diastereoselectivity (*syn:anti*, *dr* 21:1.0) (Figure 6.2.b). The isolated product **105** was also a known compound with reported ¹H NMR and ¹³C NMR data.¹⁹⁷ Hence **105** was determined to be the *anti,syn* stereotriad **V** undoubtedly.

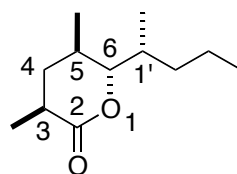


Hydrogenation of **102** with (*S*)-**Cat** provided the triad **106** with high diastereoselectivity (*syn:anti*, *dr* >99:1.0) (Figure 6.2.c). Starting from **106**, the diol **109** can be synthesized in one step (Reaction 6.2). **109** was a known compound with reported ¹H NMR and ¹³C NMR data.¹⁹⁸ Thus **106**, the hydrogenation product of **102**, was determined to be an *syn,syn* stereotriad **T**. Hydrogenation of **103** with (*R*)-**Cat** provided the triad **107** with high diastereoselectivity (*syn:anti*, *dr* 1.0:18) (Figure 6.2.d). The ¹H NMR and ¹³C NMR of the isolated product **107** was compared carefully with those of **106**.¹⁹⁷ Hence **107** was determined to be the *syn,anti* stereotriad **U** certainly.



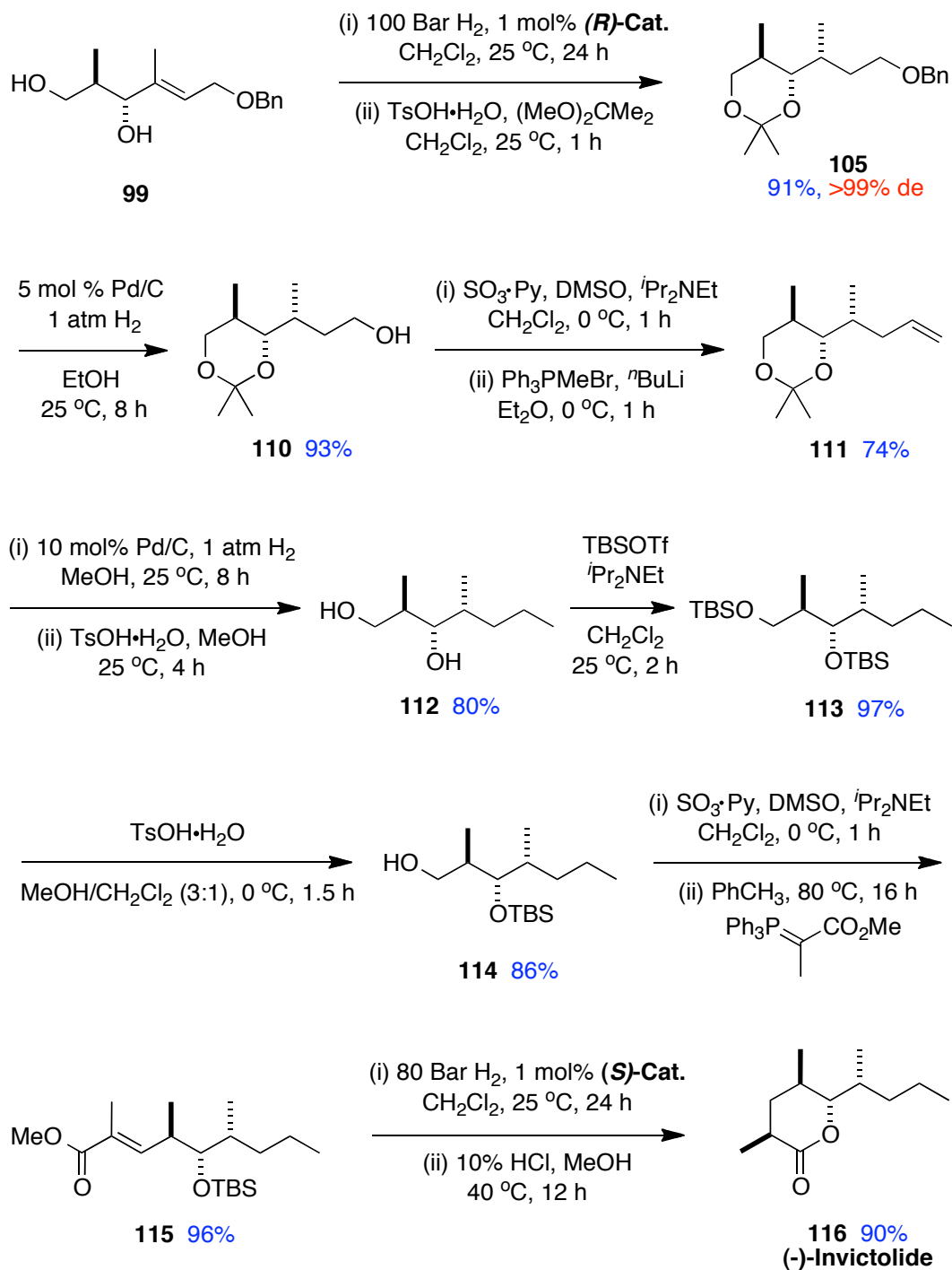
6.2.4 Total syntheses of (-)-invictolide

(-)-Invictolide was first isolated from the red imported fire ant queens as a queen recognition pheromone and its relative stereochemistry was proposed by Tumlinson and co-workers based on spectroscopic analysis and synthesis.¹⁹⁹ The absolute stereochemistry of natural (-)-invictolide was established to have (3*R*, 5*R*, 6*S*, 1'*R*)-configuration by Mori and co-worker in 1986,²⁰⁰ and both the levorotatory and the racemic forms of invictolide exhibit pheromone activity.¹⁹⁹ Owing to its' interesting structural feature having the δ -lactone moiety with four chiral centers and also to the biological activity, several syntheses have been appeared in the literature.^{199,201-205}



(-)-Invictolide

Our group has been using chiral analogs of Crabtree's catalyst in syntheses of some pivotal chirons for preparations of natural products, particularly in the polyketide series. With the previous developed methodologies for the stereotriad synthesis, we were very interested in the stereoselective synthesis of (-)-invictolide. In searching the structure of (-)-invictolide for retrosynthetic disconnections, we thought that the most straightforward way to achieve this goal was an exploitation of the triad **V** as a starting material, readily obtained from asymmetric hydrogenation. The 3*R*-methyl group should also be able to be introduced with high selectivity by using the asymmetric hydrogenation methodology developed previously in our group^{28,77} (Scheme 6.4).

Scheme 6.5. Total synthesis of (-)-invictolide.

6.3 Conclusions

Once again, this chapter demonstrated several very important issues throughout the whole period of our asymmetric hydrogenation researches. First, constructive matching of chiral Crabtree's catalyst analogs with stereochemical vectors from substrates can afford high diastereoselectivities, even in cases where Ir- or Rh-*diphosphine* complexes would probably give poor conversions and/or selectivities. Chiral analogs of Crabtree's catalyst are almost uniquely suitable for asymmetric hydrogenation of coordinating unfunctionalized, trisubstituted alkenes. In most cases our catalyst usually can give *catalyst* control for hydrogenations of chiral alkenes. On the contrary, metal diphosphine complexes only hydrogenate these substrates well if there is a coordinating functional group, in which case substrate control is usually observed. By choosing the right enantiomer of the catalyst and modifying the protecting group on the hydrogenation substrates, we are able to synthesize all the four stereotriads **T-W** with high diastereoselectivities and yields. Mechanistic complementarities enabled all eight stereoisomers of the ubiquitous chiral methyl, hydroxy, methyl fragments to be made. Compared to other traditional methods for synthesis of this type of chirons, methodologies shown here clearly demonstrate their high advantages in terms of economic efficiency, product universality, and environmental friendliness.

Using the newly developed methodology, (-)-invictolide was synthesized efficiently. Two key hydrogenation reactions have been applied to generate two chiral centers in the molecule. This not only demonstrated that this new methodology is highly practical, but also proved that our previous developed methodology can be used in much more complex system. To the best of our knowledge, this is the first catalytic method that can give all the diastereoisomers of stereotriads **T-W** with high stereoselectivities. We are looking forward to seeing the wide application of this methodology in future.

CHAPTER VII

CONCLUSIONS AND OUTLOOK

7.1 Conclusions

7.1.1 New methodologies for the syntheses of privileged chirons

Asymmetric hydrogenations of functionalized, but not coordinatively functionalized, alkenes have been used to prepare several chirons for syntheses of polyketide natural products using our *N*-carbene Crabtree's catalyst analog (Figure 7.1). Most alkene substrates were made from optically active starting materials (eg *Roche* ester, lactic acid, glyceraldehyde dimethyl ketal) and the products were optically pure. High stereoselectivities generally were obtained, even before chromatography; this was possible by matching the stereochemical preference of the catalyst with that of the substrate (we call these "catalyst- and substrate-vectors"); the catalyst vector is nearly always dominant, but the substrate vector has influence. Substrate vectors can be optimized by manipulating: (i) the functional group on the alkene (eg ester, hydroxymethyl, and alkoxymethyl); (ii) protecting groups; and, (iii) alkene geometry. Using chiral substrates that allow for these modifications via a rational approach has almost always enabled us to develop highly stereoselective reactions.

Through our studies, we have shown that chiral analogs of Crabtree's catalyst are almost uniquely suitable for asymmetric hydrogenation of coordinating unfunctionalized, trisubstituted alkenes. Metal diphosphine complexes can only hydrogenate these substrates well if there is a coordinating functional group, in which case substrate control is usually observed. We have successfully demonstrated the importance of chiral analogues of Crabtree's catalyst in acyclic stereocontrolled diastereoselective hydrogenations. Compared to other traditional methods for synthesis of these important chirons, methodologies shown here clearly demonstrate their high advantages in terms of economic efficiency, product universality, and environmental friendliness.

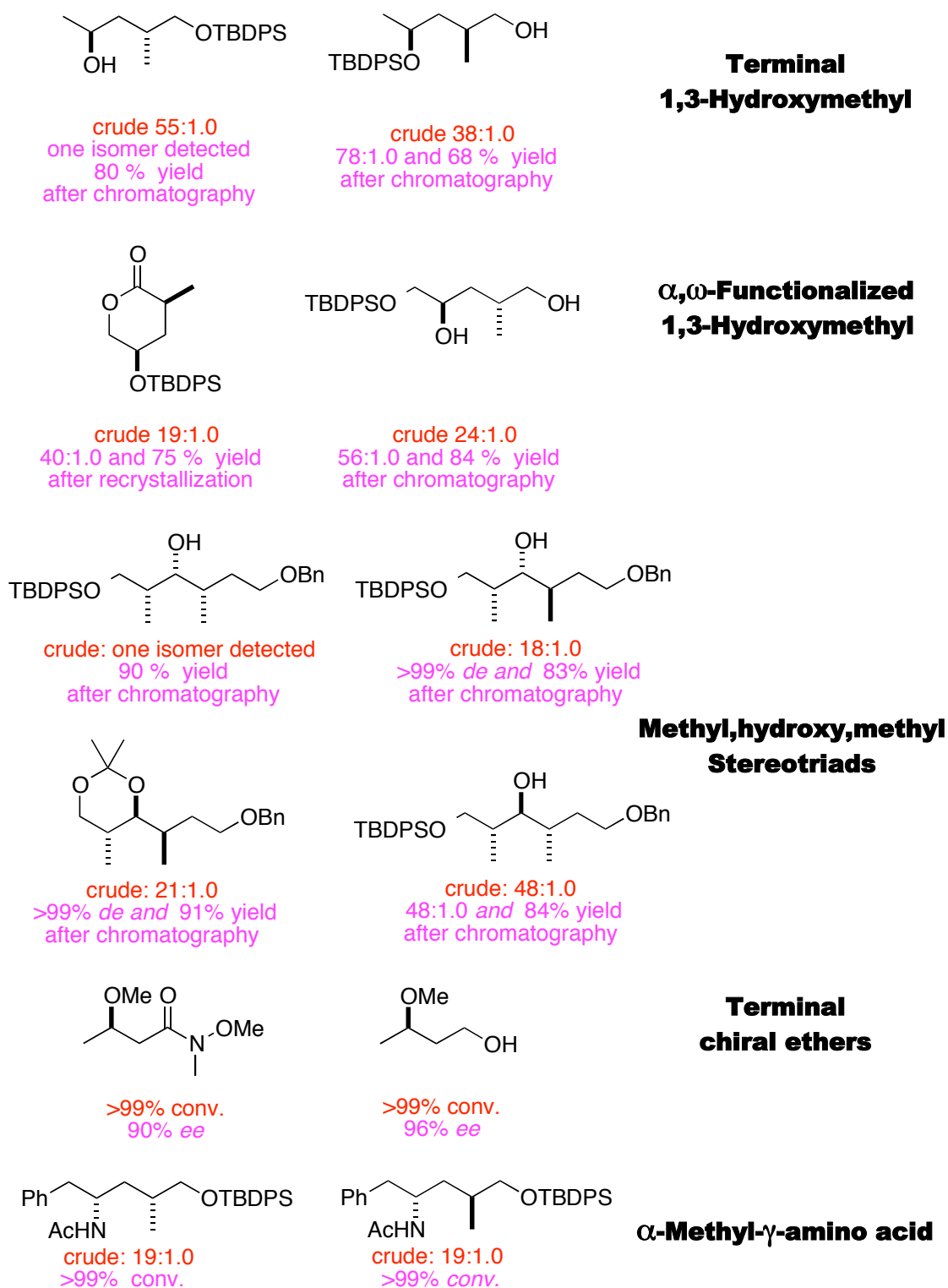


Figure 7.1. Chirons prepared via stereoselective hydrogenation.

The pivotal chirons shown in Figure 7.1 could be cornerstones of many convergent asymmetric syntheses. Figure 7.2 depicts some natural products prepared so far to illustrate our hydrogenation approach to polyketide-derived natural products. Exercises like this clearly demonstrated to the natural products syntheses community that the methodology is practical.

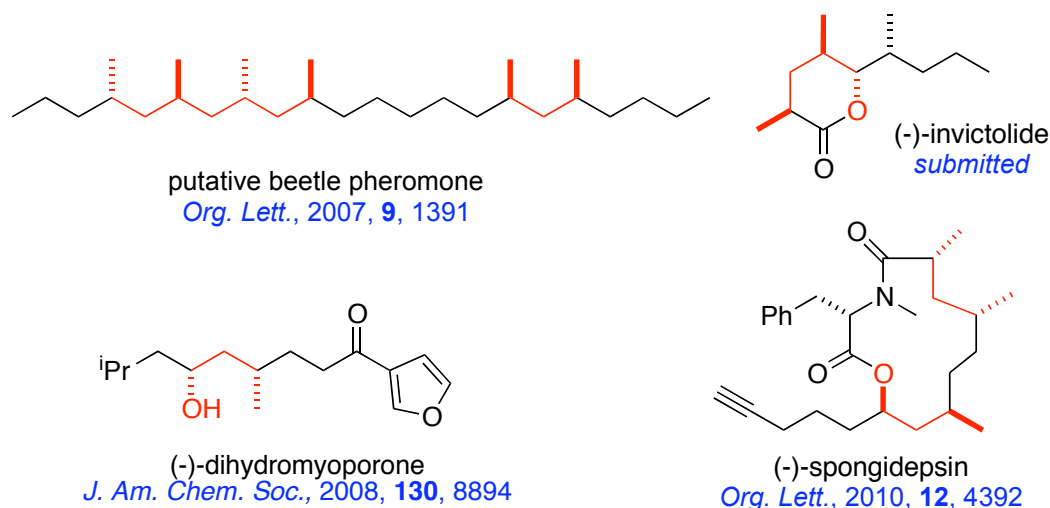
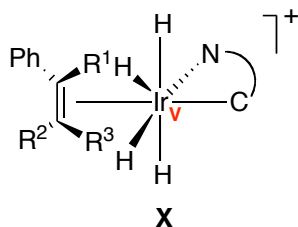


Figure 7.2. Some natural products prepared via hydrogenation reactions.

7.1.2 Acidities of metal hydrides in catalysis



The mechanism(s) of action of chiral Crabtree's catalyst (or chiral analogs) has not been experimentally proven. However, we^{24,27-29} and others³⁰ used high level DFT calculations to study the hydrogenations by chiral Crabtree catalyst analogs, and reached very similar conclusions. Basically, the metal undergoes not one but two oxidative additions of hydrogen oxidizing the Ir(1+) to a seven-coordinate Ir(5+) tetrahydride **X** ("C" here denotes carbene ligand) before rate limiting transfer of hydrogen to the coordinated alkene. This explains why only Crabtree's catalyst, and not Wilkinson's,

hydrogenates tri- and tetra-substituted alkenes at a significant rate: the metal center is more electrophilic {Ir(5+) vs Rh(3+)} and less hindered {the iridium is seven-coordinate and the four hydride ligands are small}. This also explains the insensitivity of the iridium system to air and to oxidizing solvent, since Ir(3+) and Ir(5+) tend to be more stable than Ir(1+) both to air and to oxidants in general.

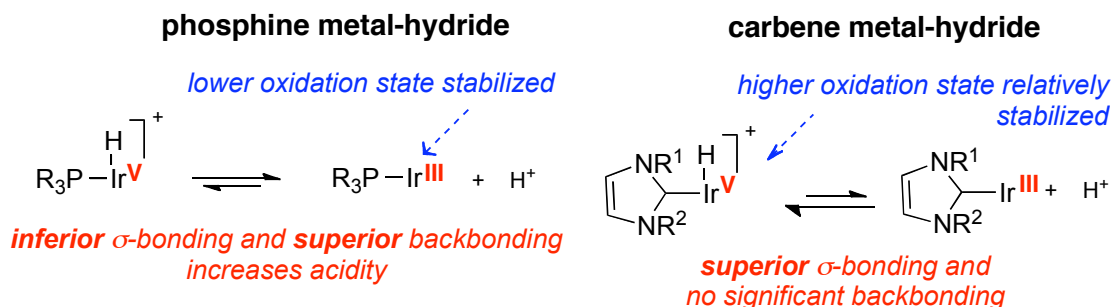


Figure 7.3. Ir-hydride intermediates in catalytic hydrogenations have markedly different acidities.

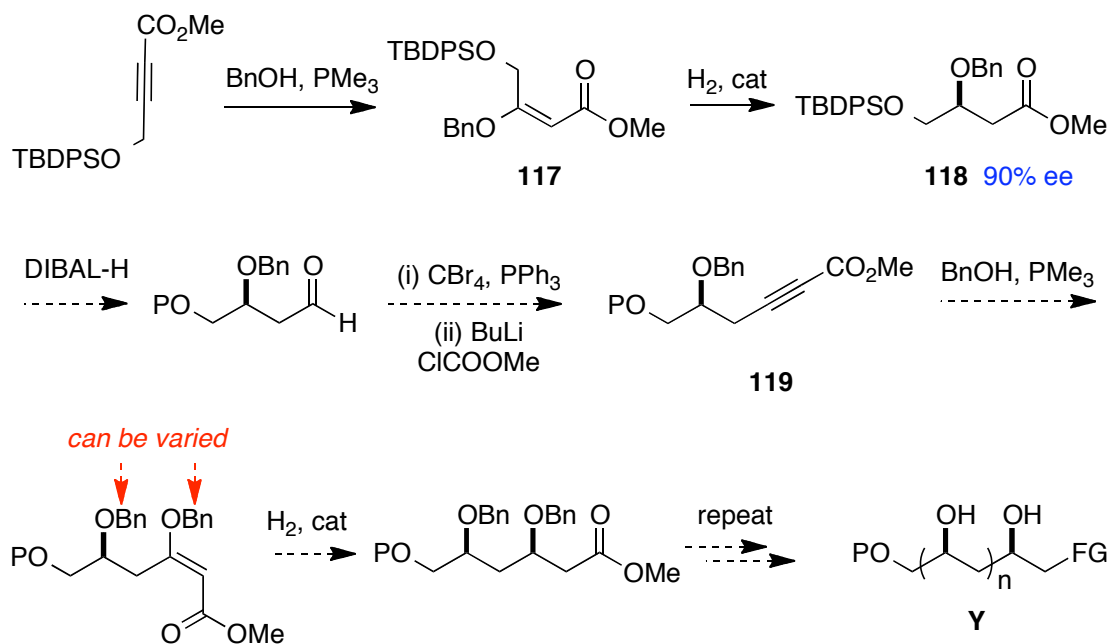
While hydrogenating enol ether substrates, we realized that protons were being generated in the catalytic process. Based on our proposed mechanism, we hypothesized that this was due to dissociation of a Ir(5+)-H bond to give Ir(3+) and a proton.⁴⁷ Further we suggested this is *more* prevalent for *N,P*-complexes than for *N,carbene*-systems, for the reasons shown in Figure 7.3. DFT calculations confirmed this, and estimated the difference for the key (ligand)Ir(5+)H₄(alkene) **X** catalytic intermediates to be stunning 7 pK_a units.²⁷ This accounts for several observations about the *N,carbene*-system relative to *N,P*-catalysts, *ie* it is: (i) *less* likely to decompose acid-sensitive alkenes; (ii) *less* likely to cause acid-mediated double bond migration before hydrogenation (as shown via deuteration experiments); (iii) unable to hydrogenate tetrasubstituted alkenes, whereas *N,P*-catalysts are, probably because of issue (ii); and, (iv) unable to initiate a red-response in the acid-base indicator methyl red, whereas hydrogenations using the *N,P*-catalysts do this. These observations indicate the Ir carbene catalyst may be well suited to acid sensitive substrates.

7.2 Outlook

7.2.1 Syntheses of other important chirons via asymmetric hydrogenations

Many polyketide-derived natural products contain acyclic 1,3-diol fragments. Existing methods for obtaining them²⁰⁷ are dominated by hydride reductions of carbonyls,²⁰⁸⁻²¹⁰ hence our proposal to form the chiral centers via hydrogenation methods is interesting for its complementary chemoselectivity. This work also further explores our recent findings that hydrogenations with *N,P*-Ir complexes generate acidic solutions, whereas our *N*,carbene-catalyst and hydrogen gives significantly less acidic solutions (by about 7 pK_a units).²⁷ For this reason, the *carbene* catalyst is more appropriate for enol ethers,⁴⁷ because *N,P*-Ir catalyst/H₂ cause decomposition of these substrates.

Scheme 7.1. Planned synthesis route to 1,3-diol and 1,3,5,...n-polyol chirons.

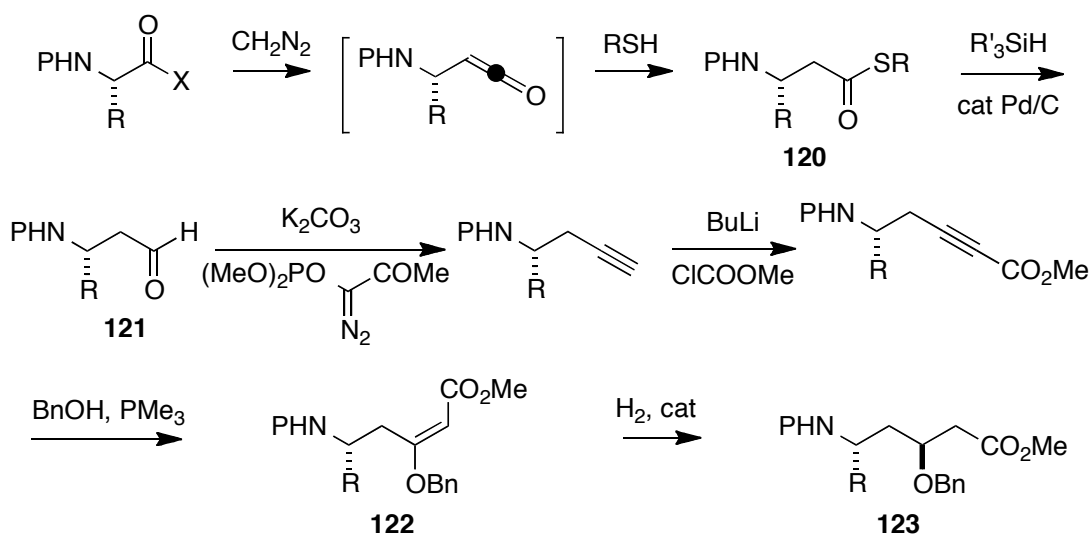


In preliminary studies, enol ether **117** was generated with high *E*-stereoselectivity (only one isomer observed by ¹H NMR) via a known method.²¹¹ This was hydrogenated to the ether **118** with high stereoselectivity. If it were critical to begin the synthesis with maximal optical purities, then similar substrates could be obtained via Noyori

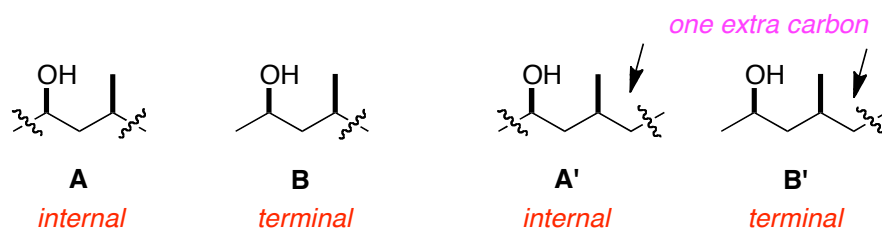
reduction of β -ketoesters.²¹²⁻²¹⁴ Reduction of the ester functionality to an aldehyde, then homologation via Corey/Fuchs^{215,216} gives an alkyne **119** to begin the iterative process as indicated. We have tested the addition of several alcohols to alkynes via the PMe_3 mediated reaction, and they all worked. Consequently, it would be easy to vary the alcohol protecting group in these schemes to maximize substrate vectors in the key asymmetric hydrogenation steps (Scheme 7.1).

By analogy with the plans for skipped polyols **Y**, amino acid starting materials could be used to produce 1,3-amino alcohols. To do this we propose to modify Seebach's Arndt-Eistert approach to homologating amino acids,²¹⁷ by using a thiol to quench the ketene intermediate. This allows facile reduction of the thioesters **120** under mild conditions.^{218,219} Homologation of these substrates would be achieved in much the same way as above (Scheme 7.2).

Scheme 7.2. Planned synthesis route to 1,3-amino alcohol chirons.



Amino alcohols are common fragments in pharmaceuticals.^{168,209,210,220-234} The *broader impact* would be the methodology to obtain these fragments from a selection of amino acids. Amino acid side-chains are excellent pharmacophores, all protein-protein interactions rely on them,²³⁵ so methods that allow diversification in medicinal chemistry beyond simple alkyl chains have merit.



Previously I have developed a good methodology for synthesis of 1,3-hydroxymethyl chirons via iridium catalyzed asymmetric hydrogenations. Through this route chiron **A** and **B** can be obtained with high yields and diastereoisomer purities (Figure 2.3).²³⁶ In this type of chirons, the chiral methyl substituent is directly connected with the functional groups. Sometimes this will bring some extra steps for further homologations. Actually literature searching has identified many natural products containing the 1,3-hydroxymethyl chirons like **A'** and **B'** that have one extra carbon between the methyl chiral center and the functional group (Figure 7.4). Hence an alternative method for synthesis of the new type of 1,3-hydroxymethyl chirons is needed.

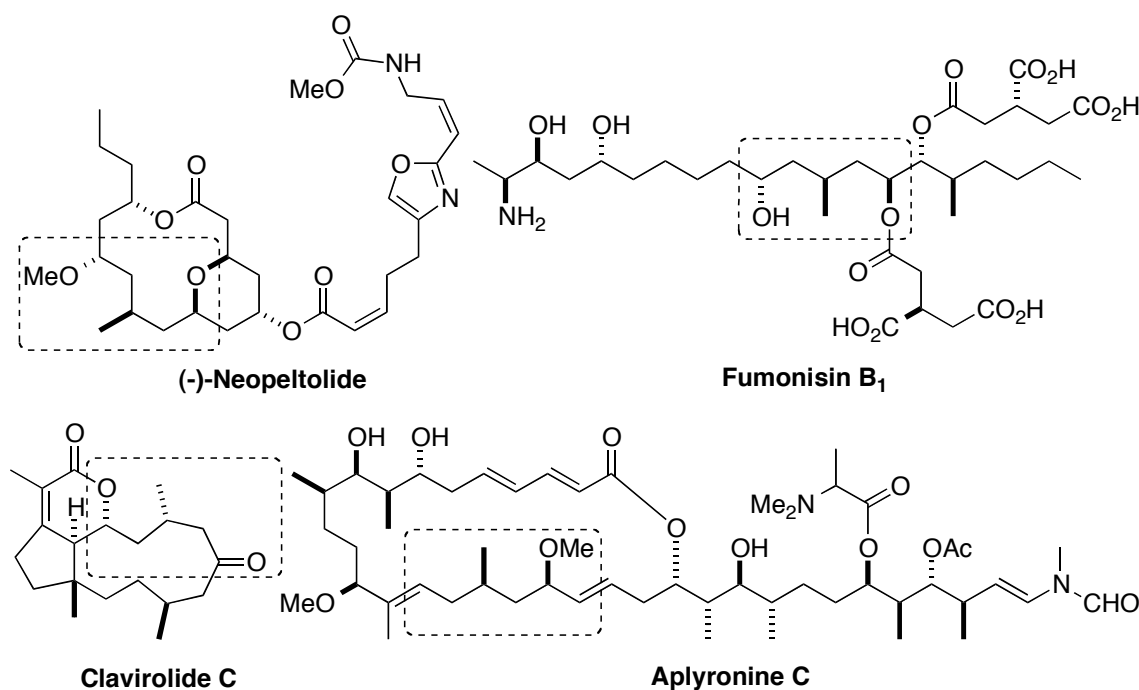


Figure 7.4. Examples of natural products that contain the new type of 1,3-hydroxymethyl fragments **A'** and **B'**.

Preliminary experiments indicate the acetate **124** is a good substrate for the hydrogenation. Based on this result, I hypothesize that alkene **125** would be a very good substrate for the synthesis of the desired new type of 1,3-hydroxymethyl chirons. By introducing a chiral acetate functional group, excellent diastereoselectivity is expected for the match case (Figure 7.5).

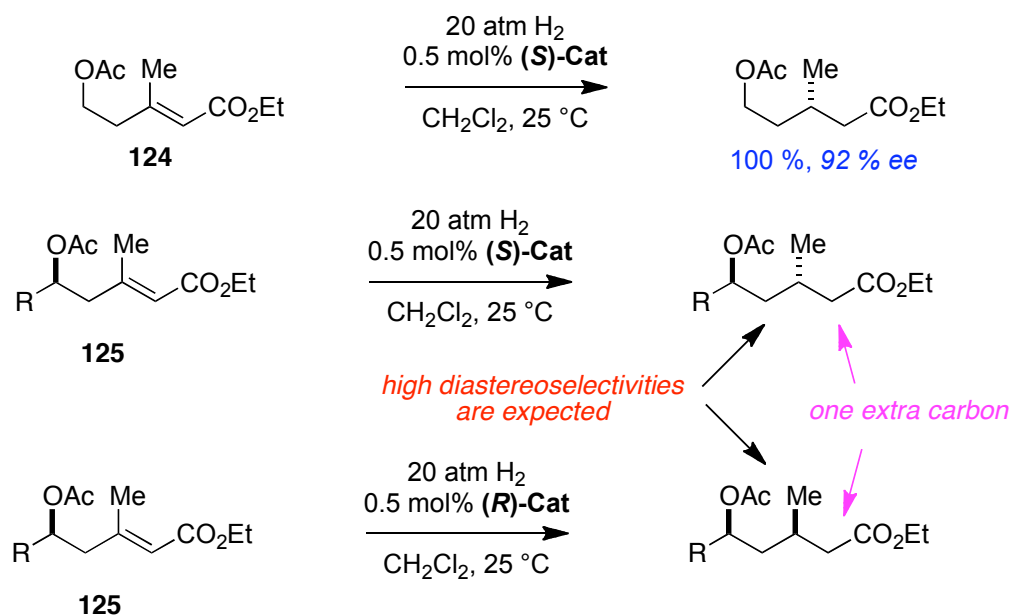


Figure 7.5. Proposed routes to the synthesis of new type of 1,3-hydroxymethyl chirons.

The hydrogenation substrates shown above can be easily synthesized through titanium catalyzed asymmetric allylation reactions followed by cross metathesis reactions¹⁰¹. The R- group can be alkyl, aromatic, heteroaromatic groups and protected alcohol can be tolerated in the reaction. Generally, high yields and very good enantioselectivities can be obtained.²³⁷ The alcohol protecting group can be easily modified at the late stage, which can greatly facilitate the diastereoselectivity optimization process (Figure 7.6).

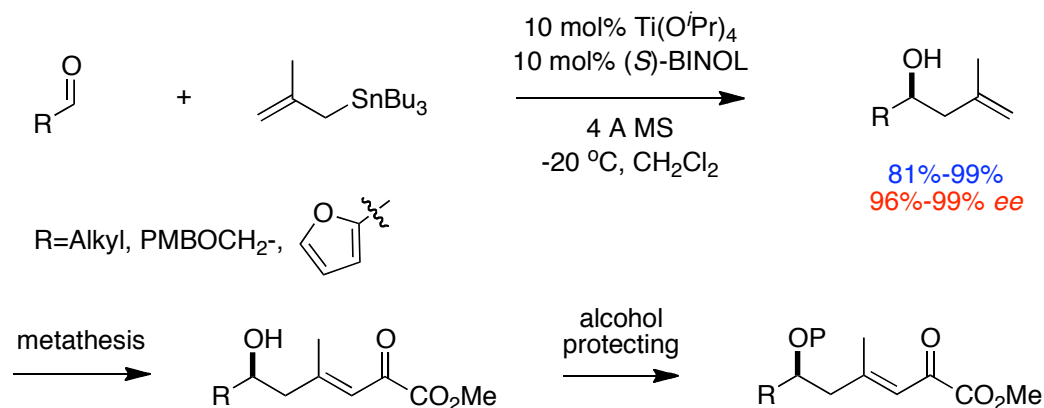


Figure 7.6. Alkene substrates synthesis for the new type of 1,3-hydroxymethyl chirons.

The importance of enantiopure 1,2-amino alcohols in asymmetric synthesis is evident from their successful application as stereochemical control elements.^{238,239} Chiral β -amino alcohols are also versatile synthons for the preparation of a wide range of biologically active natural and synthetic products such as unnatural amino acids^{239,240} (Figure 7.7). Recently, a series of chemical compounds containing the 1,2-amino alcohol fragments have been approved as HIV-1 protease inhibitors by FDA.²⁴¹

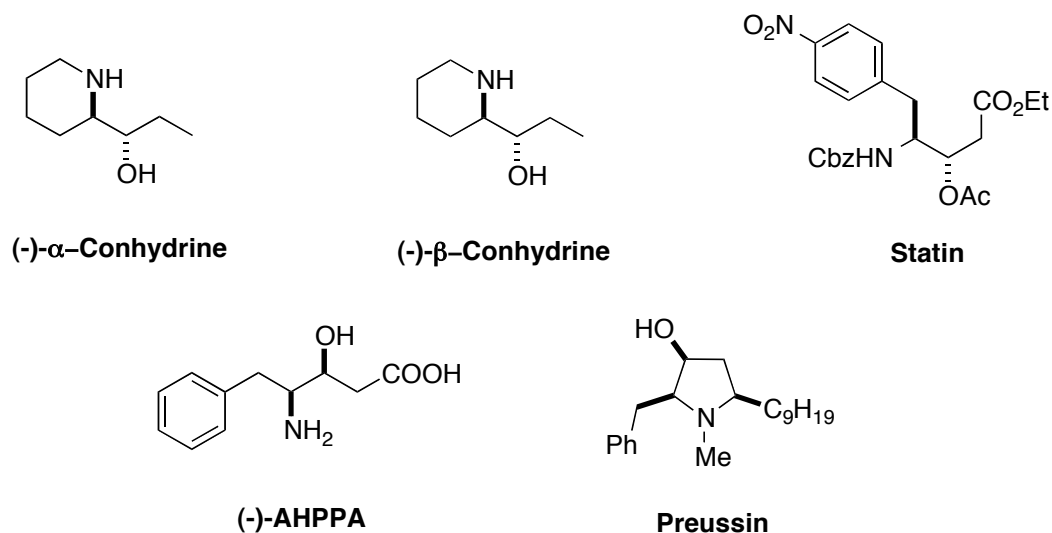


Figure 7.7. Examples of natural products containing 1,2-amino alcohol fragments.

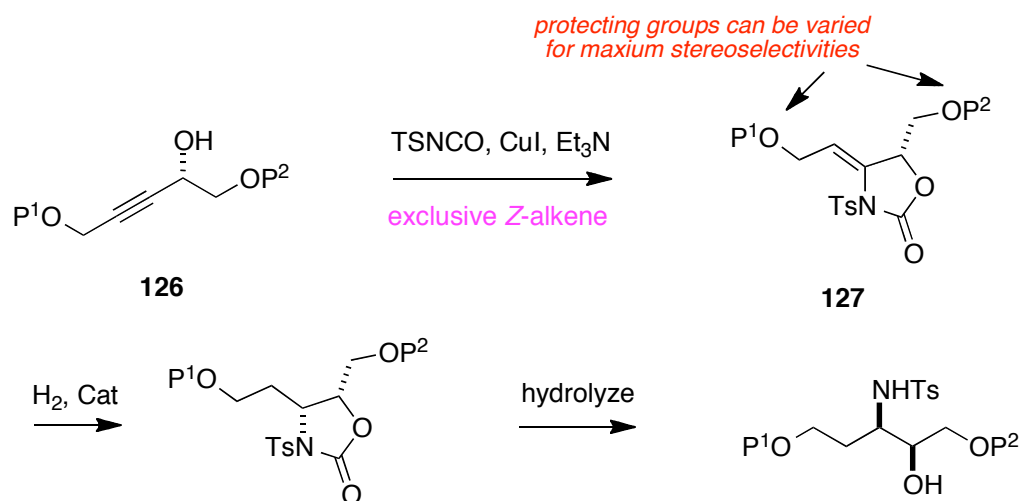


Figure 7.8. Synthesis of 1,2-amino alcohols via iridium catalyzed hydrogenations.

Figure 7.8 illustrates a route proposed to synthesize the chiral β -amino alcohols. The optical active propargylic alcohol can be synthesized from commercial available propane-1,3-diol in five step (54% overall yield, 97% *ee*).²⁴² The alcohol **126** was treated with tosyl isocyanate in the presence of a catalytic amount of CuI and Et₃N (THF, reflux) to produce the *N*-tosyl-4-(alkylidene)oxazolidin-2-one **127** (92%) as a single geometric isomer.^{243,244} By choosing the right enantiomer of the iridium catalyst and varying the protecting groups on both hydroxy groups, good diastereoselectivities for *syn*- and *anti*-isomers might be able to be achieved during the hydrogenation reactions. After hydrolysis, the chiral β -amino alcohols could be obtained readily.

Figure 7.9 shows an alternative approach to the chiral β -amino alcohols. The optical active propargylic alcohol **128** can be synthesized from commercial available an alkyl propiolate and an alkyl aldehyde in one step.^{245,246} Treating the chiral alcohol **128** with benzylamine at room temperature directly afforded the optically active 4-amion-2(5H)-furanones **129** without any racemization.²⁴⁷ This is an interesting substrate for hydrogenation, which can directly provide 1,2-amino alcohol chirons. Further, acyclic alkene substrates could also be obtained easily in one or two steps, which provides more chance to succeed in achieving good diastereoselectivities in the hydrogenation reactions.

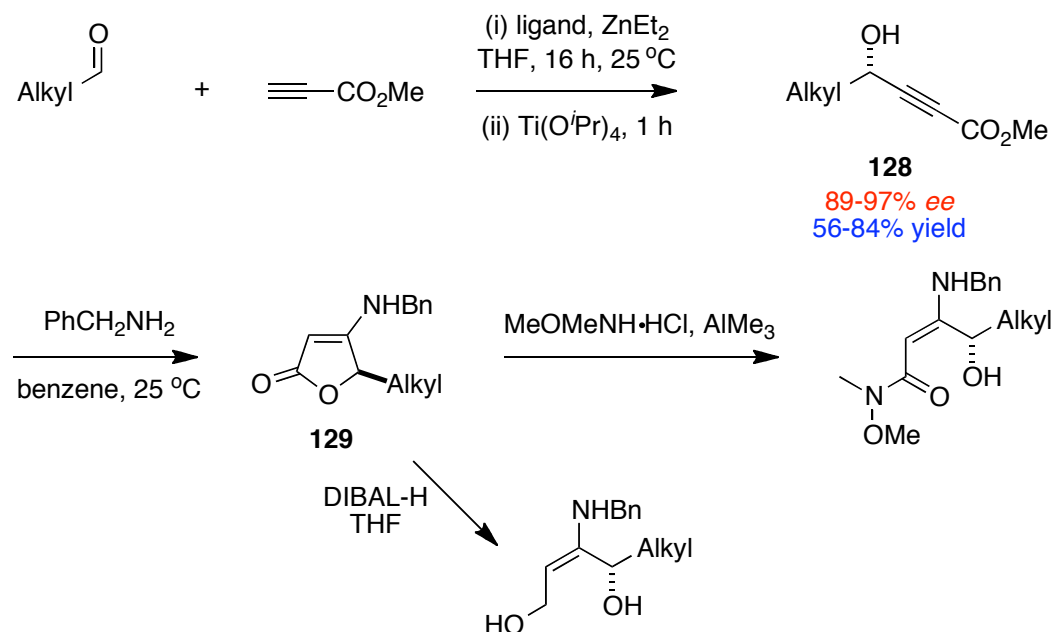
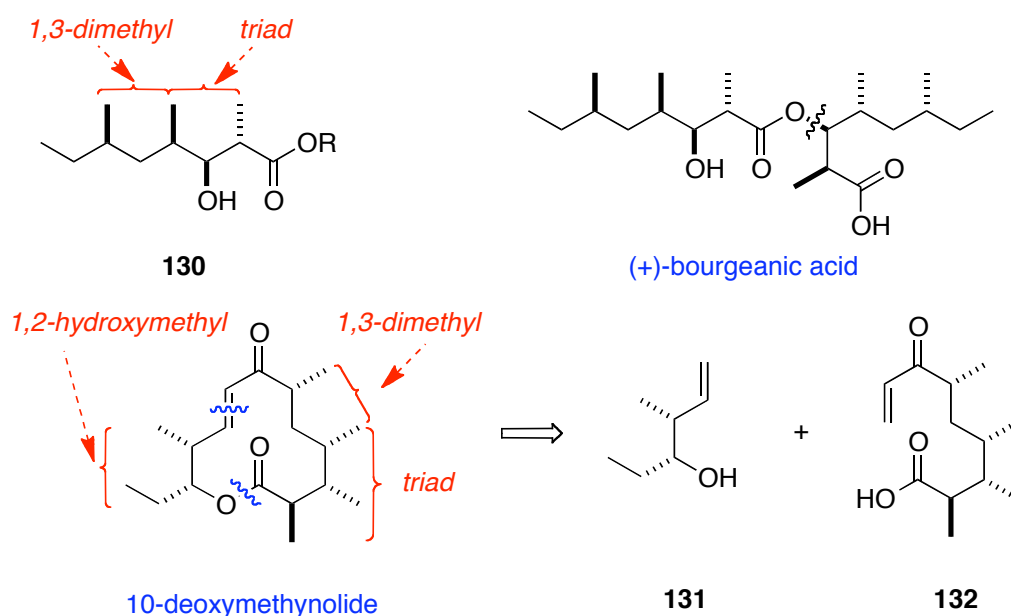


Figure 7.9. Alternative route for synthesis of 1,2-amino alcohols via iridium catalyzed hydrogenations.

7.2.2 Natural products total syntheses

During my Ph.D studies at Dr. Burgess's group, our group has developed many good methodologies for the syntheses of highly important chiral building blocks. My previous total synthesis for (-)-invictolide begins and ends with our hydrogenation methodology. A similar approach could be applied to make alcohol **130**, used in syntheses of the metabolite (+)-bourgeanic acid.²⁴⁸⁻²⁵⁰ This *alternative* target also contains 1,3-dimethyl/*anti,syn*-triad motifs. 10-Deoxymethynolide²⁵¹⁻²⁵⁴ will be made *as well as* (-)-invictolide or (+)-bourgeanic acid since it contains *three* chiral fragments that can be made via our hydrogenation approach. Fragments **131** and **132** will be joined via ester-formation then ring-closing metathesis.¹⁰¹



7.2.3 Stereo convergent synthesis of hydrogenation substrates

An aspiration for hydrogenation methodology is *practicality*. This depends on ease of access to the hydrogenation starting materials. During our previous hydrogenation studies, most of our alkene substrates are synthesized through Wittig reactions between an aldehyde and a Wittig reagent. Even though very good stereoselectivities for the double bond formation reactions (*E/Z* selectivity) can be achieved in these reactions, long reaction steps are always required due to some functional group modifications and protections. As a consequence, developing facile and stereoselective ways to the syntheses of variety of alkene substrates will be very important since this can greatly improve the practicality of the developed hydrogenation methodology.

In the previous synthesis of stereotriads **T-W**, the preparation of alkene substrates used to take 4-6 chemical transformations. Hence even the hydrogenation reactions provided very good yields and diastereoselectivities, the whole process is not very efficient considering the long steps for preparing the starting materials.

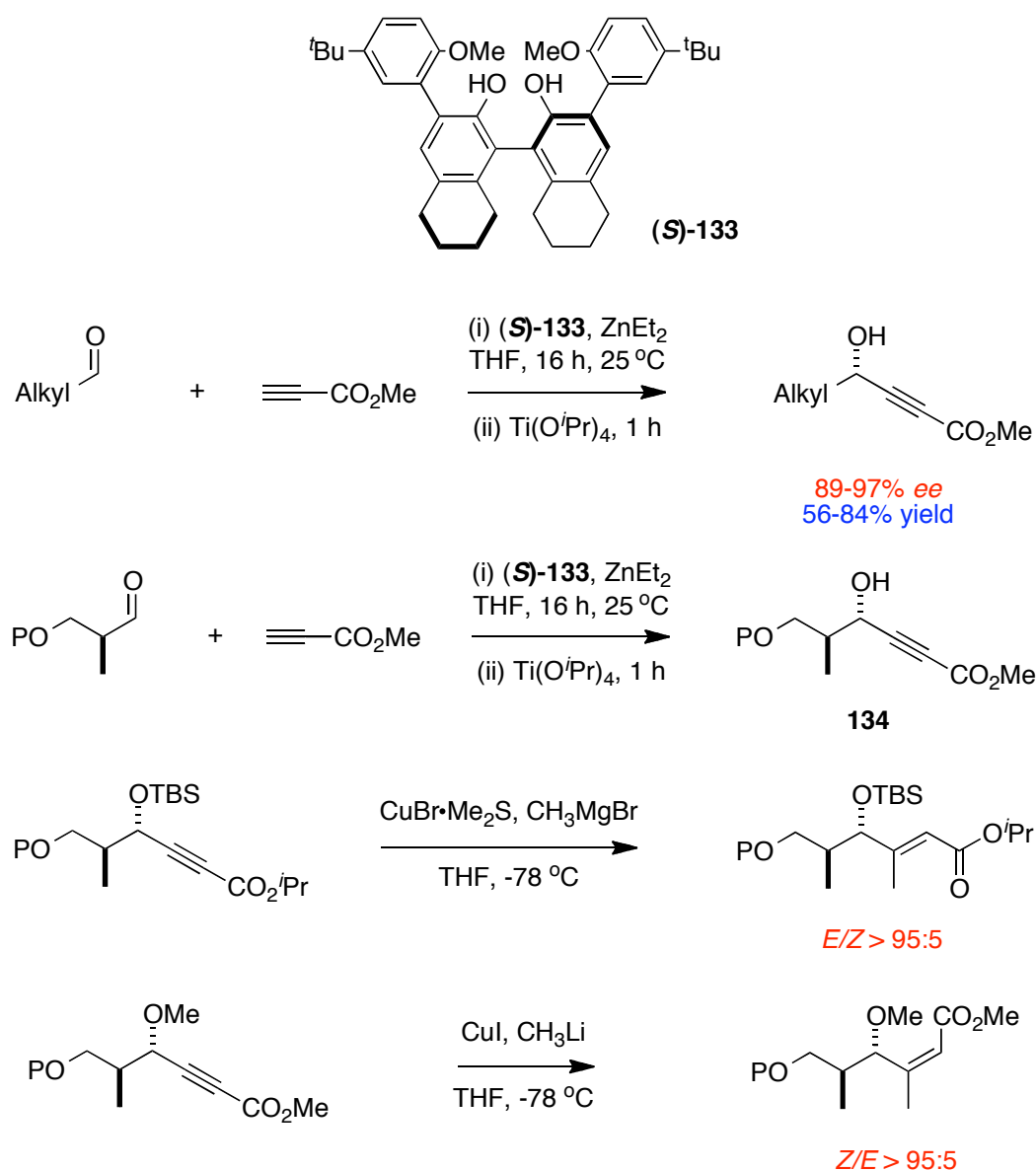


Figure 7.10. New routes for synthesis hydrogenation substrates.

Figure 7.10 illustrates one more direct and general methodology possible for preparation of many alkenes required in our hydrogenation work; this would produce *optically active substrates with defined double bond geometries in two steps*. The idea arose from a recent publication from Pu's group. A novel H₈BINOL-based chiral ligand **(S)-133** was found to catalyze the alkyl propionate addition to aliphatic aldehydes in the presence of ZnEt₂ and Ti(O^{*i*}Pr)₄ at room temperature with excellent

enantioselectivity.²⁴⁶ If the same reaction conditions are applied to a chiral aldehyde, a good diastereoselectivity should also be able to be obtained by varying the protecting group 'PG'. Thus, the key γ -hydroxy- α,β -acetylenic ester **134** could be obtained easily in one step. Subsequent methylcupration of **134** in the proper reaction conditions, both the *E*-²⁵⁵ and *Z*-allylic alcohols²⁵⁶ can be obtained with high purity.

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APPENDIX A

GENERAL EXPERIMENTAL PROCEDURES

General Experimental Methods

All reactions were carried out under an atmosphere of dry nitrogen. Glasswares were oven-dried prior to use. Unless otherwise indicated, common reagents or materials were obtained from commercial source and used without further purification. All the solvents were used after appropriate distillation or purification.

Flash column chromatography was performed using silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck silica gel plates with QF-254 indicator and visualized by UV. IR spectra were recorded on a Bruker Tensor 27 spectrometer. Optical rotations were measured on Jasco DIP-360 digital polarimeter.

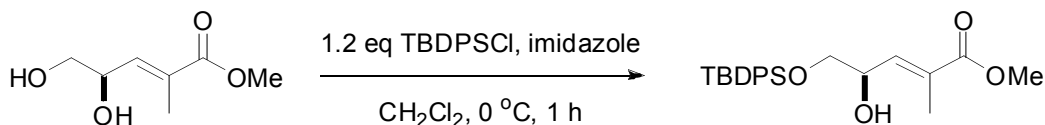
^1H and ^{13}C spectra were recorded on a Varian 300 (300 MHz ^1H ; 75 MHz ^{13}C) or Varian 500 (500 MHz ^1H ; 125 MHz ^{13}C) spectrometer at room temperature. Chemical shifts were reported in ppm relative to the residual CDCl_3 (δ 7.28 ppm ^1H ; δ 77.0 ppm ^{13}C) CD_3OD (δ 3.31 ppm ^1H ; δ 49.0 ppm ^{13}C). Coupling constants (J) were reported in Hertz.

General Catalytic Hydrogenation Conditions

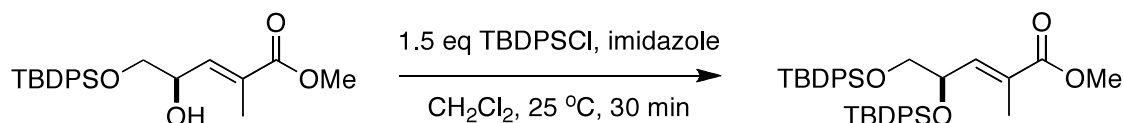
The alkene was dissolved in CH_2Cl_2 (0.5 M) and the iridium catalyst (**(S)-1** or **(R)-1**) (1 mol%) was then added. The resulting solution was degassed by three cycles of freeze-pump-thaw using nitrogen, then transferred to a Parr Bomb. The bomb was flushed with hydrogen for 1 min without stirring. The mixture was then stirred at 700 rpm under 50 atm of H_2 . After 4 h, the bomb was vented and the solvent was evaporated. The crude product was passed through a silica plug ($\text{EtOAc}/\text{hexanes}$ = 3/7). The enantiomeric and diastereomeric ratios of the crude materials were then measured via chiral capillary GC or HPLC analysis.

APPENDIX B

EXPERIMENTAL DATA FOR CHAPTER II

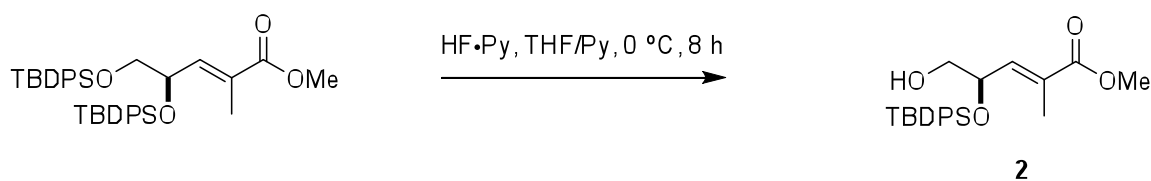
**(*R,E*)-Methyl 5-(*tert*-Butyldiphenylsilyloxy)-4-hydroxy-2-methylpent-2-enoate**

Imidazole (0.40 g, 5.85 mmol) was added in one portion to a stirred, solution of (*R,E*)-methyl 4,5-dihydroxy-2-methylpent-2-enoate (0.72 g, 4.50 mmol) in CH₂Cl₂ (20 mL) at 0 °C. *t*-Butyldiphenylsilyl chloride (1.48 g, 5.40 mmol) was added slowly over *ca* 5 min. After 1 h stirring at 0 °C, the reaction mixture was quenched by addition of saturated NaHCO₃ aqueous solution (10 ml). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 10 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography eluting with EtOAc/hexanes (20%) gave the allylic alcohol (1.63 g, 91%) as a colorless oil. $[\alpha]_D^{23} +10.90$ (*c* 1.47, CHCl₃); IR (neat) 3468 (br), 3049, 2951, 2929, 2862, 1717, 1650, 1427, 1228, 1108, 745, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.67 (m, 4H), 7.50-7.39 (m, 6H), 6.65 (dd, *J* = 1.5, 8.1 Hz, 1H), 4.60-4.55 (m, 1H), 3.74 (s, 3H), 3.70-3.60 (m, 2H), 2.81 (br, 1H), 1.76 (d, *J*=1.5 Hz, 1H), 1.11 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 167.9, 139.0, 135.5, 132.8, 132.7, 130.1, 130.0, 129.9, 127.8 (2 peaks), 69.5, 66.4, 51.9, 26.8, 19.2, 12.9. HRMS (ESI): Exact mass calcd for C₂₃H₃₁O₄Si [M+H]⁺ 399.1992. Found 399.1994.



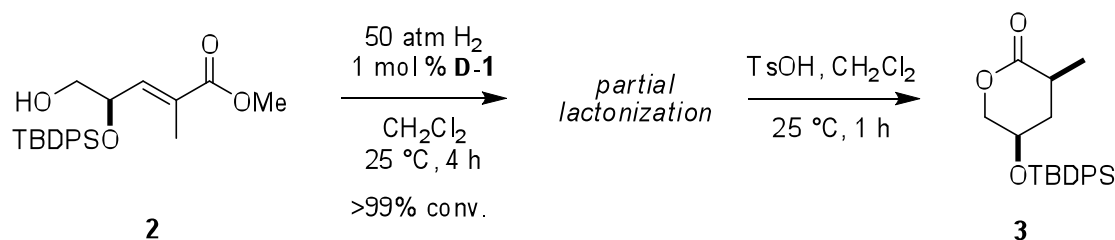
(*R,E*)-Methyl 4,5-bis(*tert*-Butyldiphenylsilyloxy)-2-methylpent-2-enoate

Imidazole (0.83 g, 12.2 mmol) and *t*-butyldiphenylsilyl chloride (2.50 g, 9.10 mmol) were added sequentially to a stirred solution of (*R*)-*E*-methyl 5-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-2-methylpent-2-enoate (2.43 g, 6.10 mmol) in CH₂Cl₂ (20 mL) at 25 °C. After 30 min stirring at 25 °C, the reaction mixture was quenched by addition of saturated NaHCO₃ aqueous solution (10 ml). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography eluting with EtOAc/hexanes (5%) gave the target ester (3.69 g, 95%) as colorless oil. $[\alpha]_D^{23}$ -31.50 (*c* 3.40, CHCl₃); IR (neat) 3075, 2952, 2935, 2862, 1714, 1426, 1105, 1075, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.81-7.70 (m, 8H), 7.44-7.40 (m, 12H), 6.69 (dd, *J* = 1.5, 8.7 Hz, 1H), 4.70-4.67 (m, 1H), 3.86-3.83 (m, 1H), 3.76 (s, 3H), 3.66-3.63 (m, 1H), 1.45 (d, *J* = 1.2 Hz, 3H), 1.15 (s, 9H), 1.09 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 168.0, 141.5, 135.9, 135.8, 135.5 (2 peaks), 133.6, 133.5, 133.2, 129.6 (3 peaks), 128.2, 127.6 (2 peaks), 127.5, 127.4, 71.2, 67.3, 51.7, 26.9, 26.8, 26.7, 19.2, 19.1, 12.7. HRMS (ESI): Exact mass calcd for C₃₉H₄₉O₄Si₂ [M+H]⁺ 637.3169. Found 637.3156.



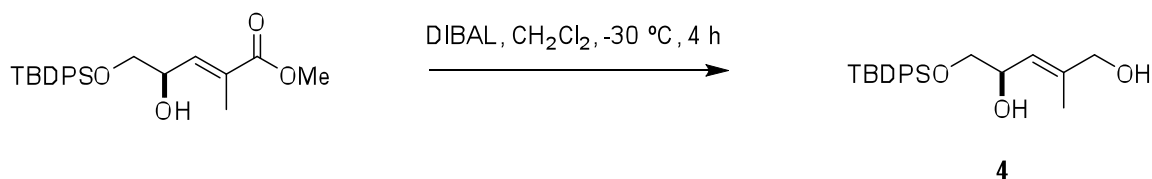
(*R,E*)-Methyl 4-(*tert*-Butyldiphenylsilyloxy)-5-hydroxy-2-methylpent-2-enoate (2)

Hydrogen fluoride pyridine (0.19 ml) and pyridine (0.40 ml) were added to a solution of (*R,E*)-methyl 4,5-bis(*tert*-butyldiphenylsilyloxy)-2-methylpent-2-enoate (0.64 g, 1.01 mmol) in THF (5 mL) at 0 °C slowly. After 8 h stirring at 0 °C, the reaction was quenched with saturated NaHCO₃ aqueous solution (5 ml). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 10 ml). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. Purification by flash chromatography eluting with EtOAc/hexanes (5%) recovered starting material 0.15 g (77% conv.) then eluting with EtOAc/hexanes (25%) gave **2** (0.28 g, 92%) as a colorless oil. $[\alpha]_D^{23}$ -70.40 (*c* 1.84, CHCl₃); IR (neat) 3468 (br), 3072, 3047, 2952, 2932, 2860, 1714, 1658, 1432, 1253, 1105, 1083, 706 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.67 (m, 4H), 7.50-7.33 (m, 6H), 6.60 (d, *J* = 1.5, 8.7 Hz, 1H), 4.60-4.55 (m, 1H), 3.68 (s, 3H), 3.65-3.40 (m, 2H), 2.11 (br, 1H), 1.40 (d, *J*=1.2 Hz, 1H), 1.07 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 167.8, 140.0, 135.8, 135.1, 133.2, 133.1, 129.9(2 peaks) 128.9, 127.8, 127.6, 71.4, 66.0, 51.8, 26.9, 19.2, 12.6. HRMS (ESI): Exact mass calcd for C₂₃H₃₀LiO₄Si [M+Li]⁺ 405.2073. Found 405.2126.



(3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxy)-3-methyltetrahydro-2*H*-pyran-2-one (3)

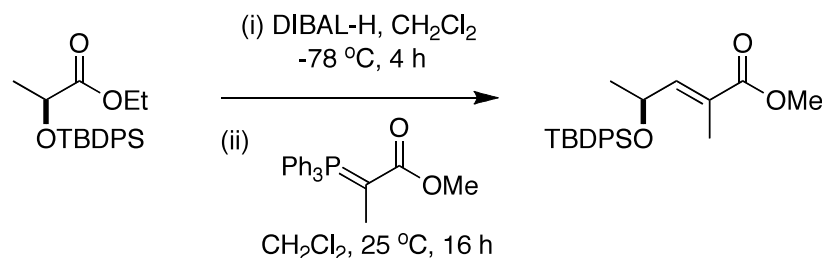
Hydrogenation of **2** (159 mg, 0.40 mmol) was carried out according to the general procedure using **D-1** (1 mol%, 6.4 mg) in CH₂Cl₂ (0.8 mL). NMR of the crude product showed 100% conversion and partial lactonization. Thus without isolation, the reaction mixture was diluted with CH₂Cl₂ (1 mL) then TsOH monohydrate (2 mg, 0.01 mmol) was added. After 1 h, saturated aqueous NaHCO₃ solution (2 mL) was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. GC analysis of the derivative of this material (see GC section later in the supporting information) gives a *cis:trans* lactone in a ratio of 19:1.0. Further recrystallization (Et₂O) gave *cis*-lactone **3** as a white crystal (109 g, 75%; *cis:trans* = 40:1.0 by GC analysis). $[\alpha]^{23}_{\text{D}} +29.4$ (*c* 1.41, CHCl₃); IR (neat) 3072, 2962, 2859, 1750, 1683, 1455, 1110, 1057, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.69-7.65 (m, 4H), 7.48-7.42 (m, 6H), 4.15-4.09 (m, 3H), 2.43-2.22 (m, 2H), 1.74-1.65 (m, 1H), 1.26 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) 174.7, 135.6 (2 peaks), 133.2 (2 peaks), 130.0 (2 peaks), 127.8 (2 peaks), 72.5, 65.6, 37.3, 32.8, 26.7, 19.0, 16.7. HRMS (ESI): Exact mass calcd for C₂₂H₂₈LiO₃Si [M+Li]⁺ 375.1968. Found 375.2072.



(*R,E*)-5-(*tert*-Butyldiphenylsilyloxy)-2-methylpent-2-ene-1,4-diol (4)

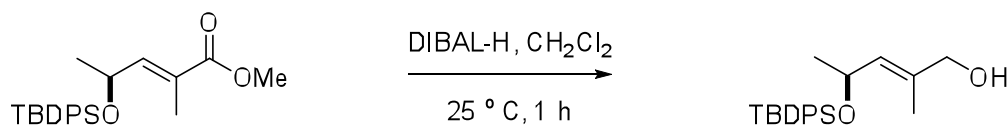
A solution of DIBAL (1 M in hexane, 7.78 mL, 7.78 mmol) was added to a solution of (*R,E*)-methyl 5-(*tert*-butyldiphenylsilyloxy)-4-hydroxy-2-methylpent-2-enoate (1.06 g, 2.66 mmol) in THF (10 mL) at -30 °C via syringe pump in a period of 30 min. The reaction mixture was stirred for an additional 4 h before dropwise addition of anhydrous EtOAc (4 mL) at -30 °C was performed. The resulting mixture was transferred quickly into a vigorously stirred mixture of hexanes/saturated potassium sodium tartrate aqueous solution (30 mL/10 mL). The solution was continued to stir for 1 h and the layers were separated. The aqueous layer was extracted with hexanes (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (50%), which gave the di-alcohol **4** (0.85 g, 86%) as a colorless oil. $[\alpha]_D^{19}$ -25.90 (*c* 0.69, CHCl₃); IR (neat) 3354 (br), 3069, 2932, 2859, 1427, 1102, 1058, 698 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.72-7.67 (m, 4H), 7.50-7.39 (m, 6H), 5.39-5.35 (m, 1H), 4.53-4.51 (m, 1H), 3.97 (s, 2H), 3.65-3.53 (m, 2H), 2.75 (br, 1H), 1.61 (br, 1H), 1.60 (s, 3H), 1.11 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 139.7, 135.5, 133.1, 133.0, 129.9, 129.8, 127.8, 122.8, 69.0, 67.8, 67.4, 26.8, 19.2, 14.0. HRMS (ESI): Exact mass calcd for C₂₂H₃₀LiO₃Si [M+Li]⁺ 377.2124. Found 377.2105.

Hydrogenation of **4** (148 mg, 0.40 mmol) was carried out according to the general procedure using D-**1** (1 mol%, 6.4 mg) in CH₂Cl₂ (0.8 mL). NMR of the crude product showed 100% conversion to **5**. GC analysis of the derivative of the crude material (see GC section later in the supporting information) showed *anti:syn* ratio to be 24:1.0. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (5%) give **5** (*anti:syn* = 56:1.0 from GC analysis) as a colorless oil (125 mg, 84%). [α]_D²¹ +8.8 (*c* 1.1, CHCl₃), (lit. [α]_D²⁵ +4.1 (*c* 1.1, CHCl₃)); IR (neat) 3351 (br), 3069, 2927, 2857, 1429, 1114, 742, 706 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.77-7.66 (m, 4H), 7.50-7.39 (m, 6H), 3.90-3.82 (m, 1H), 3.65-3.31 (m, 6H), 1.84 (br, 1H), 1.44-1.26 (m, 1H), 1.09 (s, 9H), 0.91 (d, *J*=6.9 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 135.9, 135.8, 133.3, 130.2, 128.1, 71.4, 68.9, 68.6, 38.4, 34.8, 27.1, 19.5, 18.3. HRMS (ESI): Exact mass calcd. for C₂₂H₃₂LiO₃Si [M+Li]⁺ 379.2281. Found 379.2232.

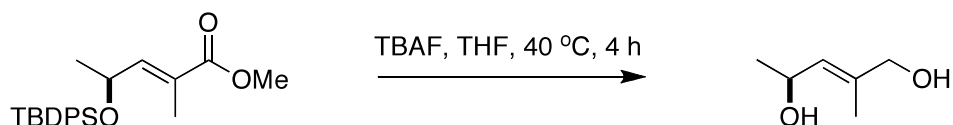


(*S,E*)-Methyl 4-(*tert*-Butyldiphenylsilyloxy)-2-methylpent-2-enoate

A solution of DIBAL (1 M in hexane, 30 mL, 30 mmol) was added to a solution of (*S*)-ethyl 2-(*tert*-butyldiphenylsilyloxy)propanoate (7.13 g, 20.0 mmol) in CH₂Cl₂ (40 mL) at -78 °C via syringe pump in a period of 1 h. The reaction mixture was stirred at -78 °C for 1h and then additional 10 ml DIBAL was introduced slowly via syringe pump. The solution was continued to stir for 1h before dropwise addition of anhydrous MeOH (10 mL) at -78 °C and then the mixture was transferred quickly into a vigorously stirred mixture of CH₂Cl₂/saturated potassium sodium tartrate aqueous solution (300 mL/100 mL). The resulting solution was stirred for 1h and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 100 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. This crude aldehyde was immediately dissolved in CH₂Cl₂ (80 mL) and the Wittig reagent (10.5 g, 30 mmol) was added in one portion at 25 °C. The reaction mixture was stirred at room temperature for 16 h then it was concentrated and added into silica gel (60 – 200 mesh). Use vacuum pump to dry the silica gel at room temperature and load the silica gel on column. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5% - 10%) gave desired ester as colorless oil (7.24 g, 95%). GC analysis of this material showed > 99% ee. (The (*R,E*)-methyl 4-(*tert* butyldiphenylsilyloxy)-2-methylpent-2-enoate was synthesized from commercial available (*R*)-methyl lactate). [α]_D¹⁸ -51.80 (*c* 1.70, CHCl₃); IR (neat) 3075, 2951, 2857, 1720, 1423, 1245, 1110, 1071, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.62 (m, 4H), 7.43-7.35 (m, 6H), 6.74 (dd, *J*=1.5, 8.1 Hz, 1H), 4.60-4.56 (m, 1H), 3.74 (s, 3H), 1.45 (d, *J*=1.5 Hz, 3H), 1.21 (d, *J*= 6.3 Hz, 3H), 1.07 (s, 9H). ¹³C NMR (75 MHz, CDCl₃) 168.5, 145.3, 135.8, 135.7, 134.0, 133.7, 129.6(2 peaks), 127.6, 127.5, 125.3, 66.7, 51.8, 26.9, 23.1, 19.1, 12.2. HRMS (ESI): Exact mass calcd. for C₂₃H₃₀LiO₃Si [M+Li]⁺ 389.2124. Found 389.1641.

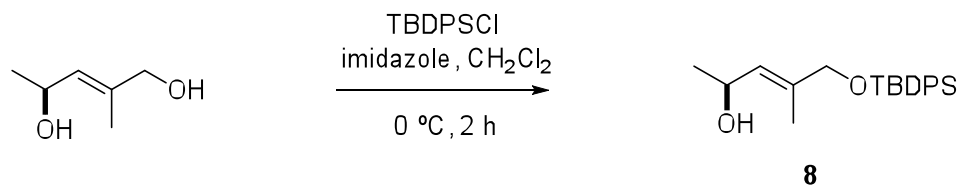
**6****(*S,E*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylpent-2-en-1-ol (6)**

A DIBAL solution (1 M in hexane, 41.6 mL, 41.6 mmol) was added to a solution of (*S,E*)-methyl 4-(*tert*-butyldiphenylsilyloxy)-2-methylpent-2-enoate (7.24 g, 18.9 mmol) in CH₂Cl₂ (40 mL) at 25 °C slowly. The reaction mixture was stirred for 1 h and then quenched with anhydrous MeOH (10 mL) and diluted with CH₂Cl₂ (100 mL) and saturated potassium sodium tartrate aqueous solution (50 mL). The resulting mixture was stirred for 1 h, and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography, eluting with EtOAc/hexanes (20%), which gave alcohol **6** (6.28 g, 94%) as a colorless oil. $[\alpha]_D^{19}$ -6.9 (*c* 1.44, CHCl₃); IR (neat) 3337 (br), 2954, 2932, 2860, 1424, 1112, 996, 783 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.72-7.67 (m, 4H), 7.43-7.36 (m, 6H), 5.42 (dd, *J*=1.2, 8.7 Hz, 1H), 4.62-4.57 (m, 1H), 3.81 (d, *J*=5.7 Hz, 2H), 1.23 (dd, *J*=1.2, 7.5 Hz, 3H), 1.00 (s, 9H), 0.98-0.91 (br, 1H). ¹³C NMR (75 MHz, CDCl₃) 135.9, 135.8, 134.7, 134.4, 133.5, 130.6, 129.5, 129.4, 127.5, 127.3, 68.3, 66.4, 26.9, 24.2, 19.1, 13.5. HRMS (ESI): Exact mass calcd. for C₂₂H₃₀LiO₂Si [M+Li]⁺ 361.2175. Found 361.2127.



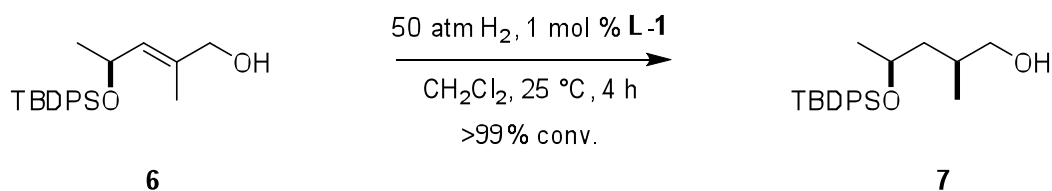
(*S,E*)-2-Methylpent-2-ene-1,4-diol

A solution of TBAF (1 M in THF, 4.70 mL, 4.70 mmol) was added to a solution of **6** (1.10 g, 3.10 mmol) in THF (10 mL) was slowly at 25 °C. The reaction mixture was raised to 40 °C and continued to stir for 4 h. After cooling the solution to room temperature, saturated NH₄Cl aqueous solution (5 mL) was added followed by Et₂O (10 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified via flash chromatography on silica gel, eluting with EtOAc/hexane (80 - 100%), which gave diol as a colorless oil (0.25 g, 71%). $[\alpha]_D^{19}$ -14.4 (*c* 1.11, CHCl₃); IR (neat) 3323 (br), 2968, 2918, 2867, 1452, 1374, 1061, 1004, 857 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 5.51 (dd, *J* = 1.5, 8.4 Hz, 1H), 4.67-4.62 (m, 1H), 4.03 (s, 2H), 1.73 (s, 3H), 1.67-1.61 (m, 2H), 1.28 (d, *J* = 6.3 Hz, 3H. ¹³C NMR (75 MHz, CDCl₃) 136.8, 129.3, 68.2, 64.7, 23.8, 14.1. HRMS (ESI): Exact mass calcd. for C₆H₁₂LiO₂ [M+H]⁺ 123.0997. Found 123.1013.



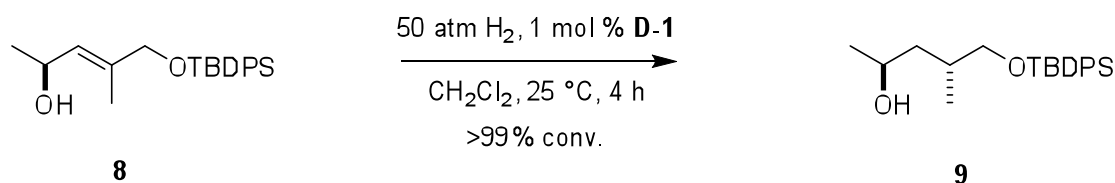
(*S,E*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methylpent-3-en-2-ol (8**)**

Imidazole (0.19 g, 2.8 mmol) was added to a stirred solution of (*S,E*)-2-methylpent-2-ene-1,4-diol (0.25 g, 2.3 mmol) in CH_2Cl_2 (10 mL) at 0 °C in one portion. *t*-butyldiphenylsilyl chloride (0.70 g, 2.5 mmol) was then added slowly. After stirring 2 h at 0 °C, the reaction mixture was quenched by addition of saturated NaHCO_3 aqueous solution (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (15%), and gave the allylic alcohol **8** (0.59 g, 74%) as a colorless oil. $[\alpha]_{\text{D}}^{18}$ -15.8 (*c* 1.51, CHCl_3); IR (neat) 3346 (br), 3072, 2963, 2865, 1427, 1111, 1052, 700 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.72-7.68 (m, 4H), 7.48-7.37 (m, 6H), 5.54 (dd, J = 1.5, 8.7 Hz, 1H), 4.67-4.57 (m, 1H), 4.07 (s, 2H), 1.66 (s, 3H), 1.29 (br, 1H), 1.26 (d, J = 6.3 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 136.0, 135.6, 133.6 (2 peaks), 129.6, 128.1, 127.6, 68.1, 64.4, 26.8, 26.7, 23.4, 19.3, 13.6. HRMS (ESI): Exact mass calcd for $\text{C}_{22}\text{H}_{30}\text{LiO}_2\text{Si}$ $[\text{M}+\text{Li}]^+$ 361.2175. Found 361.2178.



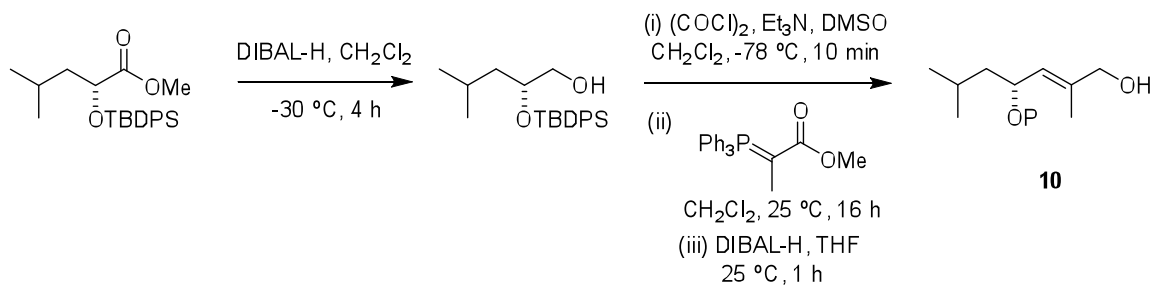
(2*S*,4*S*)-4-(*tert*-Butyldiphenylsilyloxy)-2-methylpentan-1-ol (7)

Hydrogenation of **6** (142 mg, 0.40 mmol) was carried out according to the general procedure using L-1 (1 mol%, 6.4 mg) in CH₂Cl₂ (0.8 mL). NMR of the crude product showed 100% conversion to **7**. GC analysis of the derivative of the crude material (see GC section later in the supporting information) showed *syn:anti* ratio to be 38:1.0. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (3%) gave **7** (*syn:anti* = 78:1.0 from GC analysis) as a colorless oil (97 mg, 68%). $[\alpha]_{\text{D}}^{18}$ -6.3 (*c* 0.95, CHCl₃); IR (neat) 3359 (br), 3069, 2960, 2934, 2853, 1429, 1110, 1035, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.73-7.69 (m, 4H), 7.49-7.39 (m, 6H), 4.03-3.94 (m, 1H), 3.40-3.36 (m, 2H), 2.44-2.40 (m, 1H), 1.84-1.76 (m, 1H), 1.56-1.36 (m, 2H), 1.11 (d, *J*=6.0 Hz, 3H), 1.08 (s, 9H), 0.78 (d, *J*=6.9 Hz, 3H), 0.91 (d, *J* = 9.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 135.9 (2 peaks), 134.2, 133.9, 129.7, 129.6, 127.6, 127.5, 68.5, 68.4, 43.8, 31.9, 27.0, 22.6, 19.1, 17.7. HRMS (ESI): Exact mass calcd. for C₂₂H₃₂LiO₂Si [M+Li]⁺ 363.2332. Found 363.2299.



(2*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-methylpentan-2-ol (9)

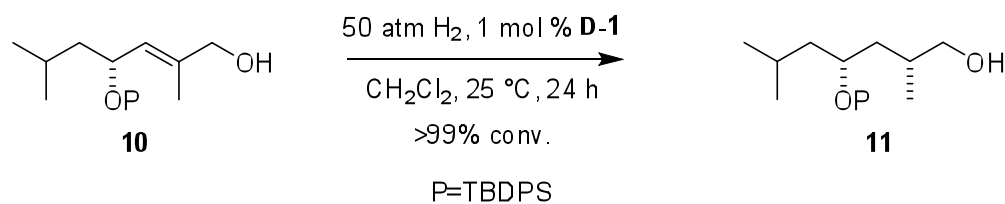
Hydrogenation of **8** (142 mg, 0.40 mmol) was carried out according to the general procedure using D-1 (1 mol%, 6.4 mg) in CH₂Cl₂ (0.8 mL). NMR of the crude product showed 100% conversion to **9**. GC analysis of the derivative of the crude material (see GC section later in the supporting information) showed *syn:anti* ratio to be 1.0:55. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (3%) gave **9** (one diastereomer from GC analysis) as a colorless oil (115 mg, 80%). $[\alpha]_{\text{D}}^{22} +8.1$ (*c* 1.47, CHCl₃); IR (neat) 3353 (br), 3066, 2957, 2932, 2862, 1424, 1108, 695 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.70-7.67 (m, 4H), 7.48-7.40 (m, 6H), 3.93-3.92 (m, 1H), 3.51 (d, *J* = 6.6 Hz, 2H), 2.61 (br, 1H), 1.90-1.84 (m, 1H), 1.56-1.33 (m, 2H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.08 (s, 9H), 0.89 (d, *J* = 6.6 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 135.6, 133.4, 130.0, 127.7, 69.9, 66.5, 44.8, 33.8, 26.8, 24.2, 19.2, 17.6. HRMS (ESI): Exact mass calcd. for C₂₂H₃₂LiO₂Si [M+Li]⁺ 363.2332. Found 363.2332.



(*R,E*)-4-(*tert*-Butyldiphenylsilyloxy)-2,6-dimethylhept-2-en-1-ol (10)

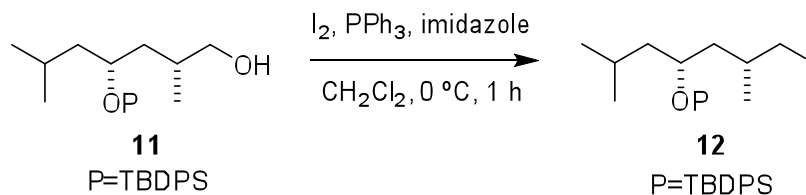
A DIBAL solution (1 M in hexane, 40 mL, 40 mmol) was added to a solution of (*R*)-methyl 2-(*tert*-butyldiphenylsilyloxy)-4-methylpentanoate (7.0 g, 18.2 mmol) in CH_2Cl_2 (40 mL) at -30°C slowly over *ca* 1 h. The reaction mixture was stirred for 4 h at -30°C before dropwise addition of anhydrous MeOH (10 mL) and dilution with CH_2Cl_2 (100 mL) and saturated potassium sodium tartrate aqueous solution (50 mL). The resulting mixture was stirred for 1 h, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography eluting with EtOAc/hexanes (15%) gave the primary alcohol (4.7 g, 73%) as a colorless oil. To a separate flask charged with $(\text{COCl})_2$ (0.24 mL, 2.7 mmol) in CH_2Cl_2 (10 mL) cooled to -78°C was added DMSO (0.31 mL, 4.4 mmol) slowly. After 5 min the previous alcohol (0.75 g, 2.1 mmol) in CH_2Cl_2 (10 mL) solution was cooled to -78°C and transferred via cannula into the previous mixture. Stirring was continued for additional 5 min at low temperature, then Et_3N (1.46 mL, 10.5 mmol) was introduced and the mixture was allowed to warm to 0°C before NH_4Cl (s) (10 mL) was added. Dilute the solution with Et_2O (25 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3×25 mL). The organic layers were combined and washed by H_2O and brine. Finally it was dried with Na_2SO_4 , filtrated, and concentrated under reduced pressure. The resulting aldehyde was used directly without further purification. This crude aldehyde was immediately dissolved in CH_2Cl_2 (20 mL) and the Wittig reagent (2.2 g, 6.3 mmol) was added in one portion at 25°C . The reaction mixture was stirred at room temperature for 16 h then it was concentrated and added into silica gel (60 – 200 mesh). Use vacuum pump to dry the silica gel at room temperature and load the silica gel on column. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5% - 10%) gave desired ester as a colorless oil (0.70 g, 79%). Finally,

the ester was dissolved in THF (5 mL) and the DIBAL (1M in hexanes, 4.1 mL, 4.1 mmol) was added slowly. The mixture was stirred at room temperature for 1 h then dropwise addition of anhydrous MeOH (2 mL) and dilution with THF (5 mL) and saturated potassium sodium tartrate aqueous solution (5 mL) was performed. The resulting mixture was stirred for 1 h, and the layers were separated. The aqueous layer was extracted with THF (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography eluting with EtOAc/hexanes (10%) gave allylic alcohol **10** (0.49 g, 75%) as a colorless oil. $[\alpha]_{\text{D}}^{19}$ -3.2 (*c* 1.22, CHCl_3); IR (neat) 3354 (br), 3043, 2960, 2860, 1424, 1110, 710 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 7.70-7.67 (m, 4H), 7.44-7.34 (m, 6H), 5.31-5.27 (m, 1H), 4.52-4.45 (m, 1H), 3.72 (d, J = 6.0 Hz, 2H), 1.68-1.52 (m, 2H), 1.33-1.25 (m, 1H), 1.18 (s, 3H), 1.05 (s, 9H), 0.83 (d, J = 6.6 Hz, 3H), 0.79 (d, J = 6.3 Hz, 3H), 0.72 (t, J = 6.6 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3) 136.0, 135.9, 135.0, 134.5, 134.4, 129.5 (2 peaks), 129.3, 127.4, 127.2, 68.5, 68.3, 47.6, 27.0, 24.2, 22.9, 22.8, 19.3, 13.6. HRMS (ESI): Exact mass calcd. for $\text{C}_{25}\text{H}_{36}\text{LiO}_2\text{Si}$ $[\text{M}+\text{Li}]^+$ 403.2645. Found 403.2636.



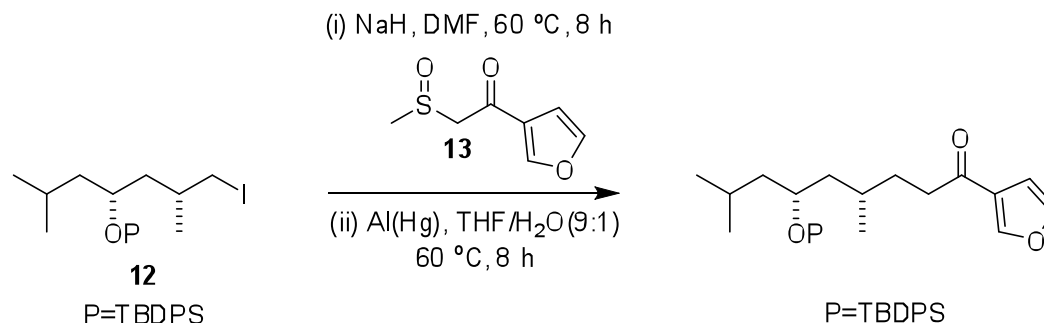
(2*R*,4*R*)-4-(*tert*-Butyldiphenylsilyloxy)-2,6-dimethylheptan-1-ol (11)

Hydrogenation of **10** (0.95 g, 2.40 mmol) was carried out according to the general procedure using **D-1** (1 mol%, 38 mg) in CH₂Cl₂ (2.4 mL). NMR of the crude product showed 100% conversion to **11**. GC analysis of the derivative of the crude material (see GC section later in the supporting information) showed *syn:anti* ratio to be 57:1.0. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (3%) give **11** (*syn:anti* = 170:1.00 from GC analysis) as a colorless oil (0.80 g, 84%). $[\alpha]_D^{20} +2.0$ (*c* 0.97, CHCl₃); IR (neat) 3348 (br), 3072, 2960, 2929, 2862, 1423, 1111, 1041, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.74-7.70 (m, 4H), 7.49-7.37 (m, 6H), 3.92-3.84 (m, 1H), 3.43-3.32 (m, 2H), 2.86 (br, 1H), 1.86-1.76 (m, 1H), 1.59-1.23 (m, 6H), 1.09 (s, 9H), 0.76 (d, *J* = 6.9 Hz, 3H), 0.70 (d, *J* = 6.0 Hz, 3H), 0.59 (d, *J* = 6.3 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 136.0 (2 peaks), 133.8, 130.0, 127.5 (2 peaks), 70.8, 68.7, 45.0, 41.3, 31.7, 27.0, 24.4, 23.0, 22.1, 19.2, 18.0. HRMS (ESI): Exact mass calcd. for C₂₅H₃₉O₂Si [M+H]⁺ 399.2719. Found 399.2747.



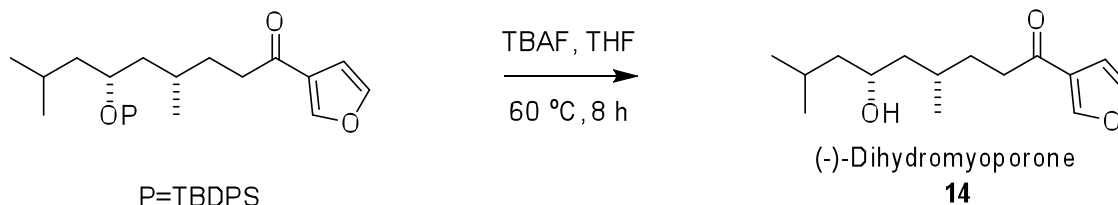
***tert*-Butyl((2*R*,4*R*)-1-iodo-2,6-dimethylheptan-4-yloxy)diphenylsilane (**12**)**

Iodine (1.02 g, 4.0 mmol) was added to a flask charged with PPh₃ (1.05 g, 4.0 mmol), imidazole (0.41 g, 6.0 mmol) and CH₂Cl₂ (5 mL) at 0 °C. After 10 min the previous alcohol solution in CH₂Cl₂ (3 mL) was added into this mixture and the flask was rinsed with CH₂Cl₂ (2 x 1mL). The solution was stirred for additional 30 min. After filtration of the precipitate and concentration, the residue was loaded on a silica gel column and flushed with hexanes to give the iodide **12** (0.94 g, 92%) as a colorless oil. $[\alpha]_D^{21} +10.1$ (*c* 1.58, CHCl₃); IR (neat) 3069, 2960, 2921, 2854, 1427, 1108, 1052, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.73-7.69 (m, 4H), 7.48 (m, 6H), 3.76-3.68 (m, 1H), 3.09 (dd, *J*= 3.6, 9.6 Hz, 1H), 2.92 (dd, *J*= 5.4, 9.6 Hz, 1H), 1.67-1.24 (m, 7H), 1.06 (s, 9H), 0.78 (d, *J*= 6.3 Hz, 3H), 0.73 (d, *J*= 6.6 Hz, 3H), 0.67 (d, *J*= 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 136.0, 135.9, 134.3, 134.2, 130.0 (2 peaks), 127.5, 127.4, 69.8, 46.6, 43.8, 30.6, 27.1, 24.5, 23.0, 22.5, 21.2, 19.4, 18.4. HRMS (ESI): Exact mass calcd. for C₂₅H₃₇ILiOSi [M+Li]⁺ 515.1818. Found 515.1900.



(4*S*,6*R*)-6-(*tert*-Butyldiphenylsilyloxy)-1-(furan-3-yl)-4,8-dimethylnonan-1-one

Sulfoxide **13** (0.77 g, 4.5 mmol) was added to a flask charged with NaH (100 mg, 4.20 mmol) and DMF (4.0 mL) at room temperature. After 10 min a solution of **12** (0.75g, 1.5 mmol) in DMF (1 mL) was added into this mixture and the flask was rinsed with DMF (2 x 0.5mL). The reaction mixture was raised to 60 °C and continued to stir for 8 h. After cooled the solution to room temperature, saturated NH₄Cl aqueous solution (5 mL) was added followed by CH₂Cl₂ (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The mixture was purified via flash chromatography on silica gel, eluting with EtOAc/hexane (50%) to give the intermediate ketofuran as a pair of diastereoisomers. These were dissolved in THF/H₂O (9:1, 18 ml), and freshly prepared Al(Hg)⁷ (ca 200 mg) was added to the solution and the mixture was heated to 60 °C and stirred for 8 h. The solution was cooled to room temperature and the precipitate was removed via filtration then washed with THF (*ca* 10 mL) thoroughly. The filtrate was dried with Na₂SO₄ and concentrated in a vacuum. The residue was loaded on a silica gel column and flushed with EtOAc/hexanes (5%) to give desired ketone (0.36 g, 49% for two steps) as a colorless oil. $[\alpha]_D^{22} +33.3$ (*c* 1.2, CHCl₃); IR (neat) 3130, 3069, 2960, 2926, 2854, 1680, 1108, 703 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 7.91 (s, 1H), 7.72-7.69 (m, 4H), 7.45 (s, 1H), 7.44-7.35 (m, 6H), 6.74 (s, 1H), 3.85-3.75 (m, 1H), 2.65-2.44 (m, 2H), 1.77-1.70 (m, 1H), 1.38-1.20 (m, 7H), 1.05 (s, 9H), 0.74 (d, *J*= 4.8 Hz, 3H), 0.72 (d, *J*= 4.5 Hz, 3H), 0.61 (d, *J*= 6.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 195.3, 146.9, 144.1, 136.0, 134.7, 134.4, 129.4 (2 peaks), 127.7, 127.6, 127.4 (2 peaks), 108.6, 70.1, 46.4, 44.9, 38.0, 31.5, 29.1, 27.0, 24.3, 23.2, 22.4, 19.4, 19.3. HRMS (ESI): Exact mass calcd. for C₃₁H₄₂LiO₃Si [M+Li]⁺ 497.3063. Found 497.3063.

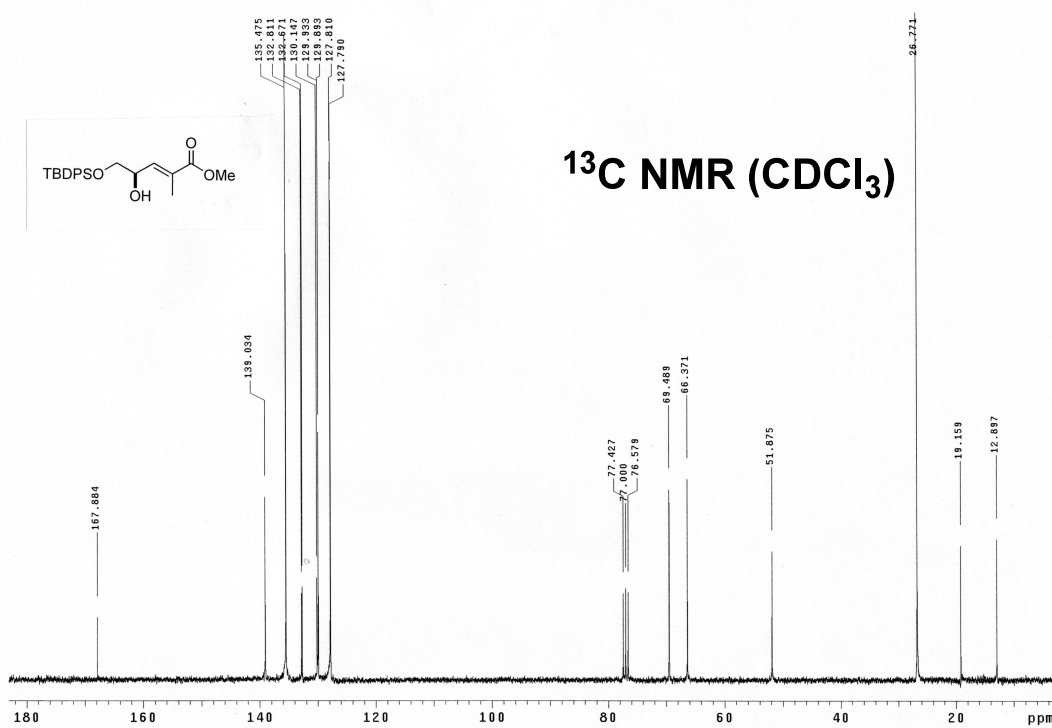


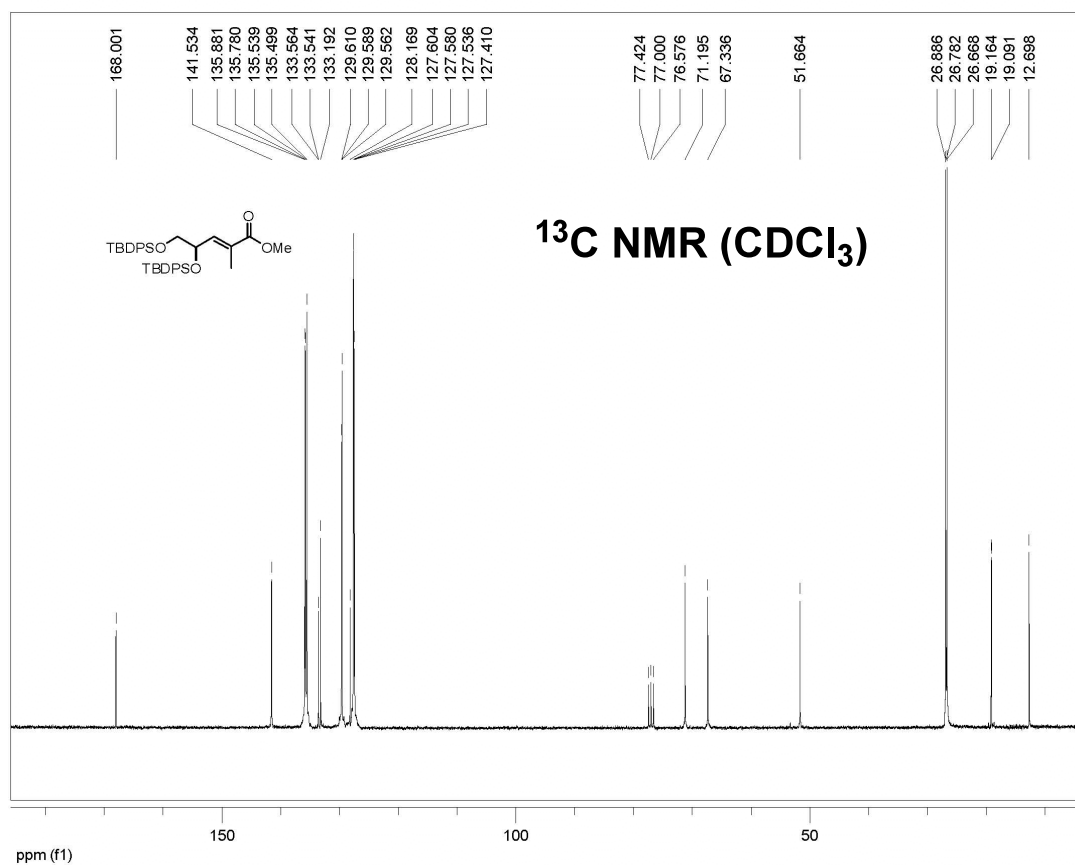
(4*S*,6*R*)-1-(Furan-3-yl)-6-hydroxy-4,8-dimethylnonan-1-one (14)

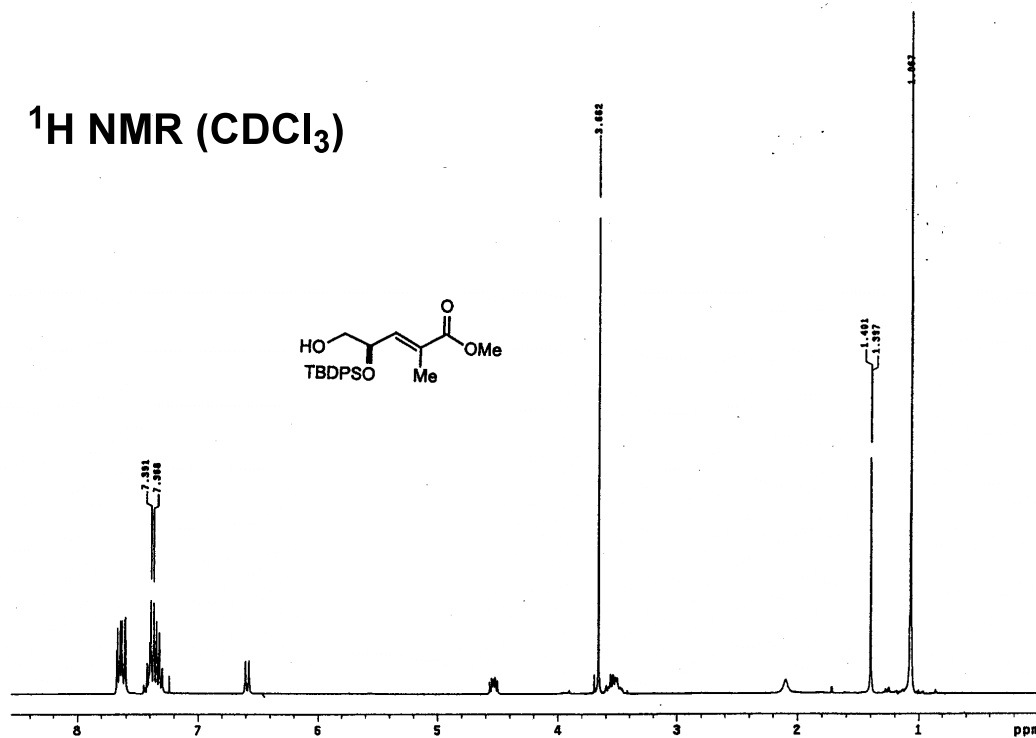
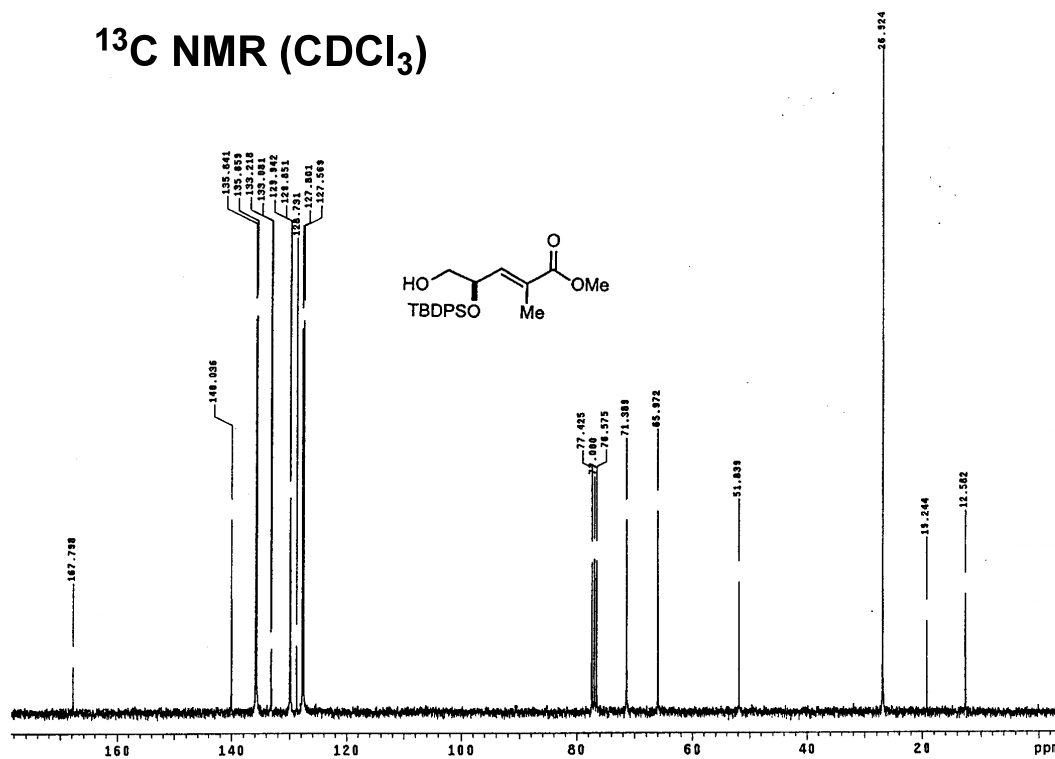
A solution of TBAF (1 M in THF, 1.48 mL, 1.48 mmol) was added to a solution of (4*S*,6*R*)-6-(*tert*-butyldiphenylsilyloxy)-1-(furan-3-yl)-4,8-dimethylnonan-1-one (0.36 g, 0.74 mmol) in THF (1.5 mL) over 5 min. The reaction mixture was raised to 60 °C then stirred for 8 h. After cooled the solution to room temperature, saturated NH₄Cl aqueous solution (3 mL) was added followed by THF (10 mL). The layers were separated and the aqueous layer was extracted with THF (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification was performed via flash chromatography on silica gel, eluting with EtOAc/hexane (20%) gave **14** as a colorless oil (0.17 g, 91%). $[\alpha]^{20}_{\text{D}} -4.2$ (*c* 1.49, CHCl₃), (lit.⁶ $[\alpha]^{25}_{\text{D}} -6.4 \pm 1.5$ (*c* 1.1, CHCl₃)); IR (neat) 3343 (br), 3133, 2957, 2918, 2865, 1670, 1561, 1465, 1152, 870 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 8.05 (m, 1H), 7.45 (m, 1H), 6.78 (m, 1H), 3.89-3.86 (m, 1H), 2.84-2.78 (m, 2H), 2.02-1.64 (m, 4H), 1.45-1.18 (m, 5H), 0.97-0.92 (m, 9H). ¹³C NMR (75 MHz, CDCl₃) 195.6, 147.0, 144.2, 127.7, 108.6, 67.3, 47.0, 45.5, 37.8, 29.8, 29.1, 24.6, 23.6, 22.1, 20.4. HRMS (ESI): Exact mass calcd. for C₁₅H₂₄LiO₃ [M+Li]⁺ 259.1885. Found 259.1885.

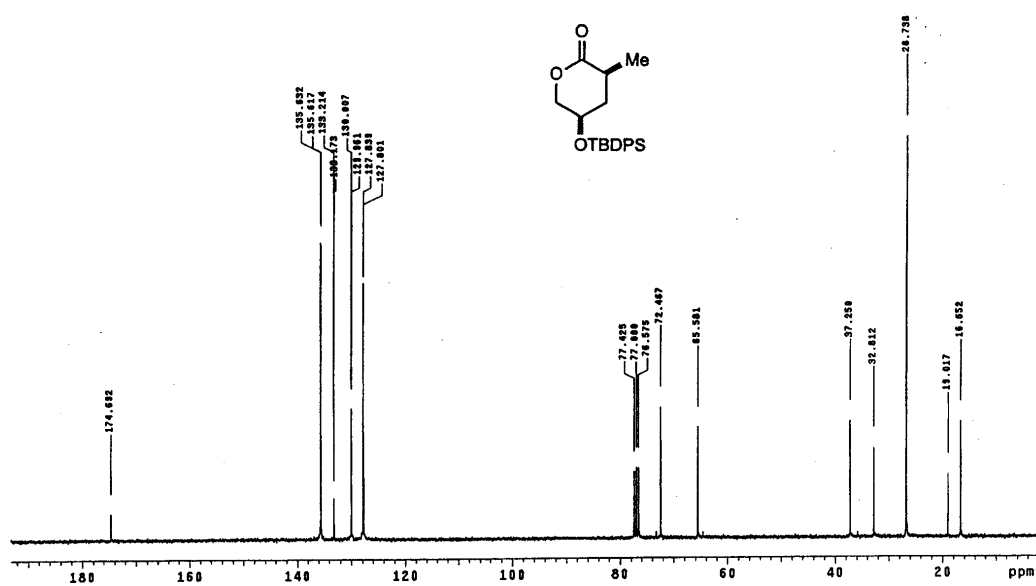
Table B-1. Comparison of ^{13}C NMR of natural and synthetic **14**

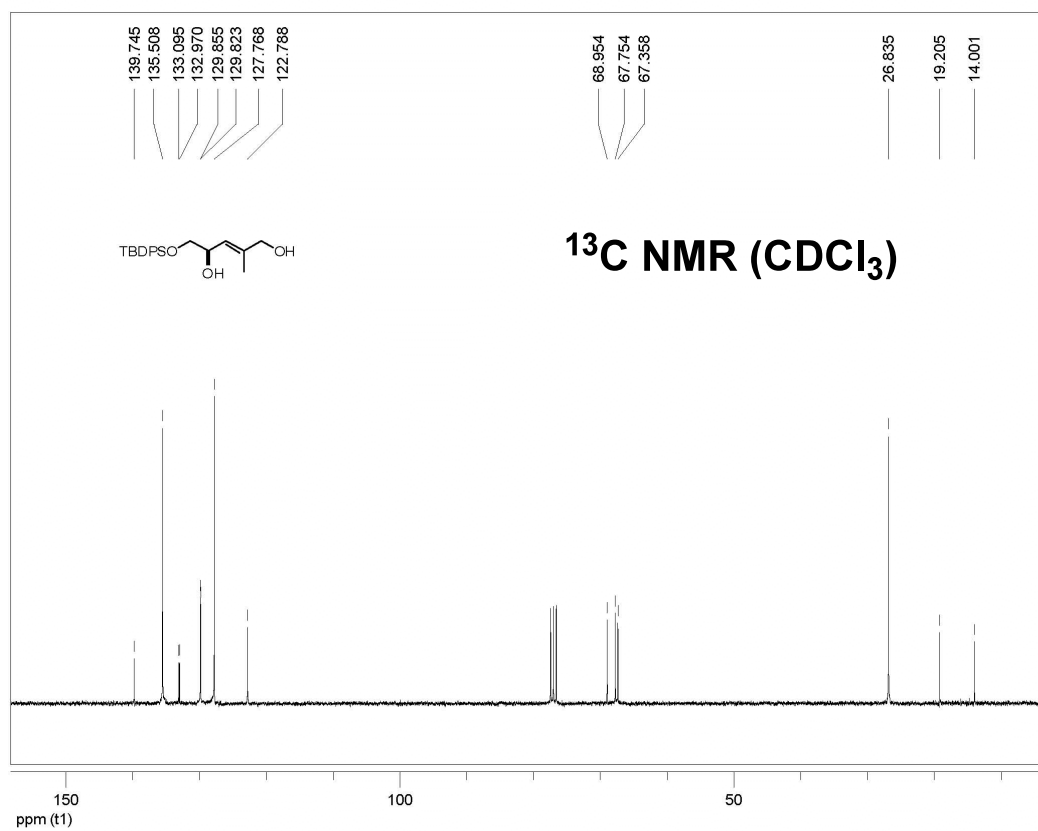
Atom number	Synthetic	Natural
C1	20.3	20.3
C2	22.0	22.0
C3	23.5	23.4
C4	24.5	24.5
C5	29.0	29.1
C6	29.8	30.0
C7	37.8	37.8
C8	45.5	45.5
C9	47.0	47.0
C10	67.3	67.4
C11	108.6	108.6
C12	127.7	Missing
C13	144.1	144.1
C14	147.0	147.0
C15	195.6	195.6

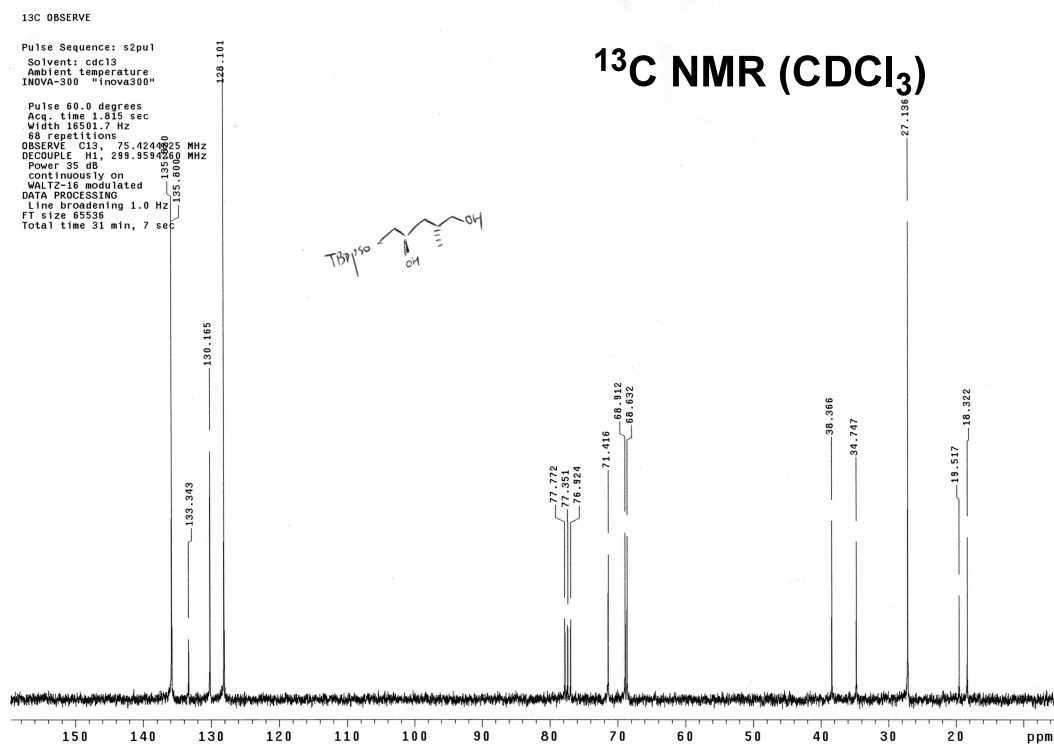


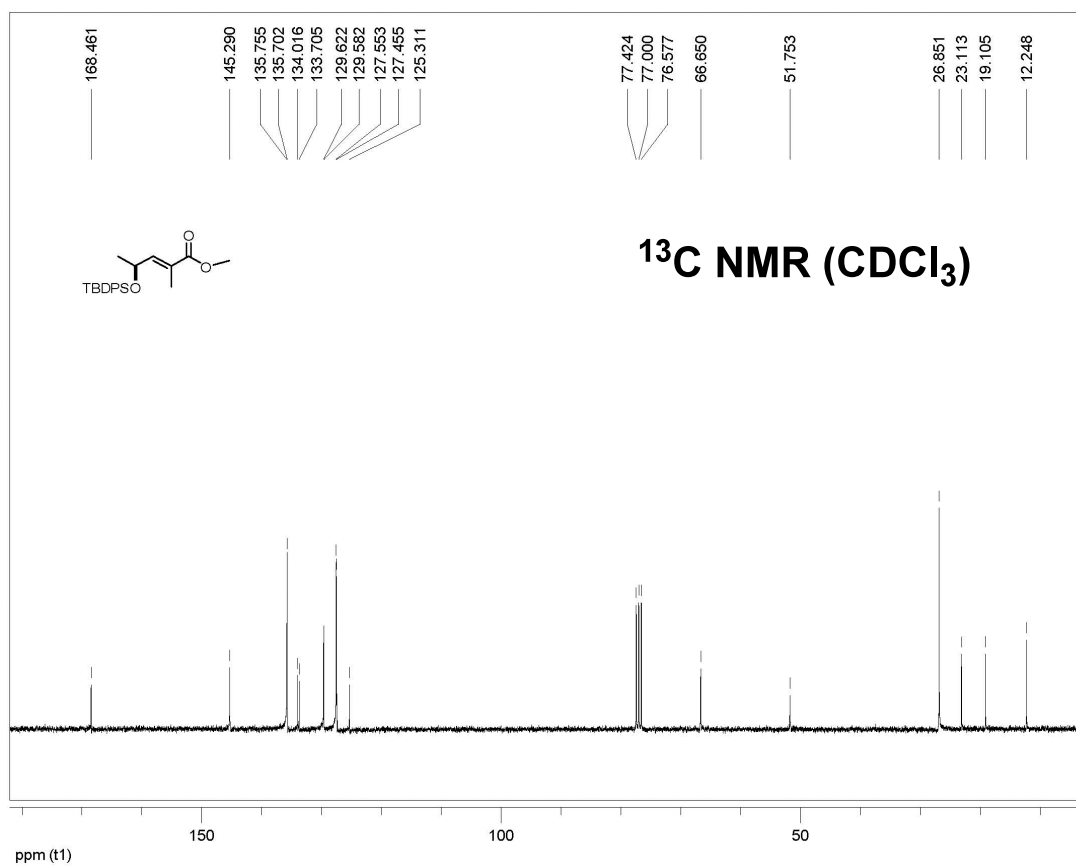
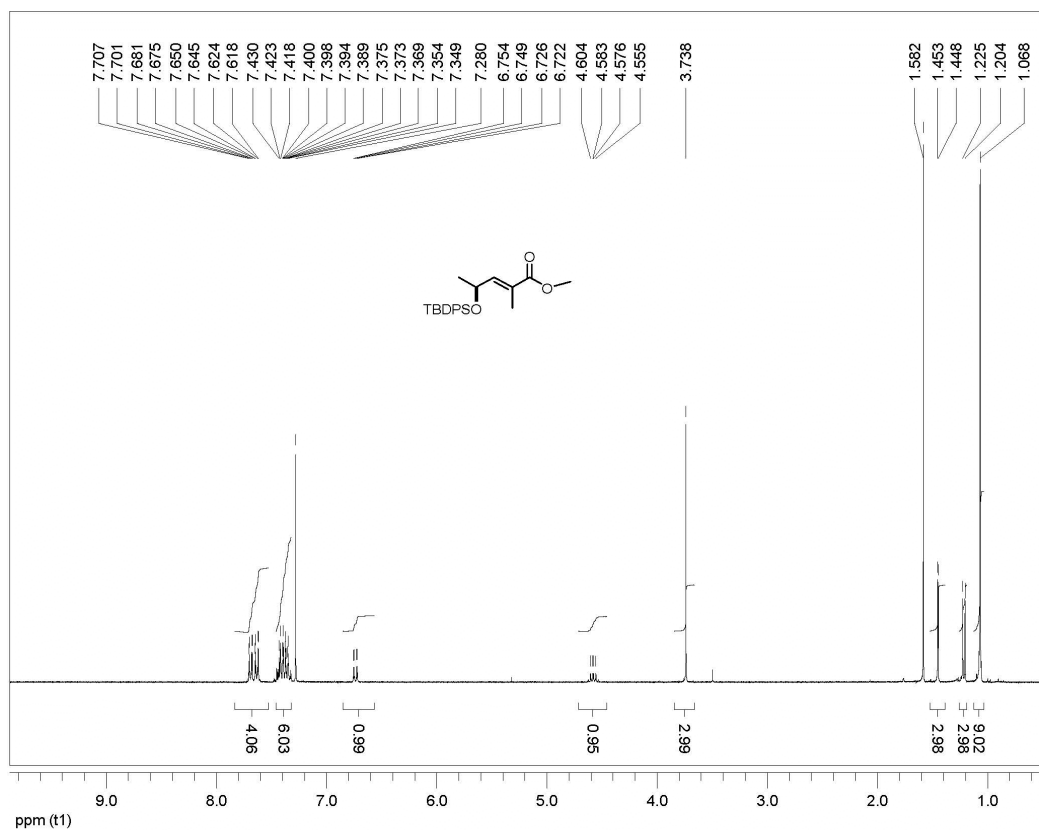


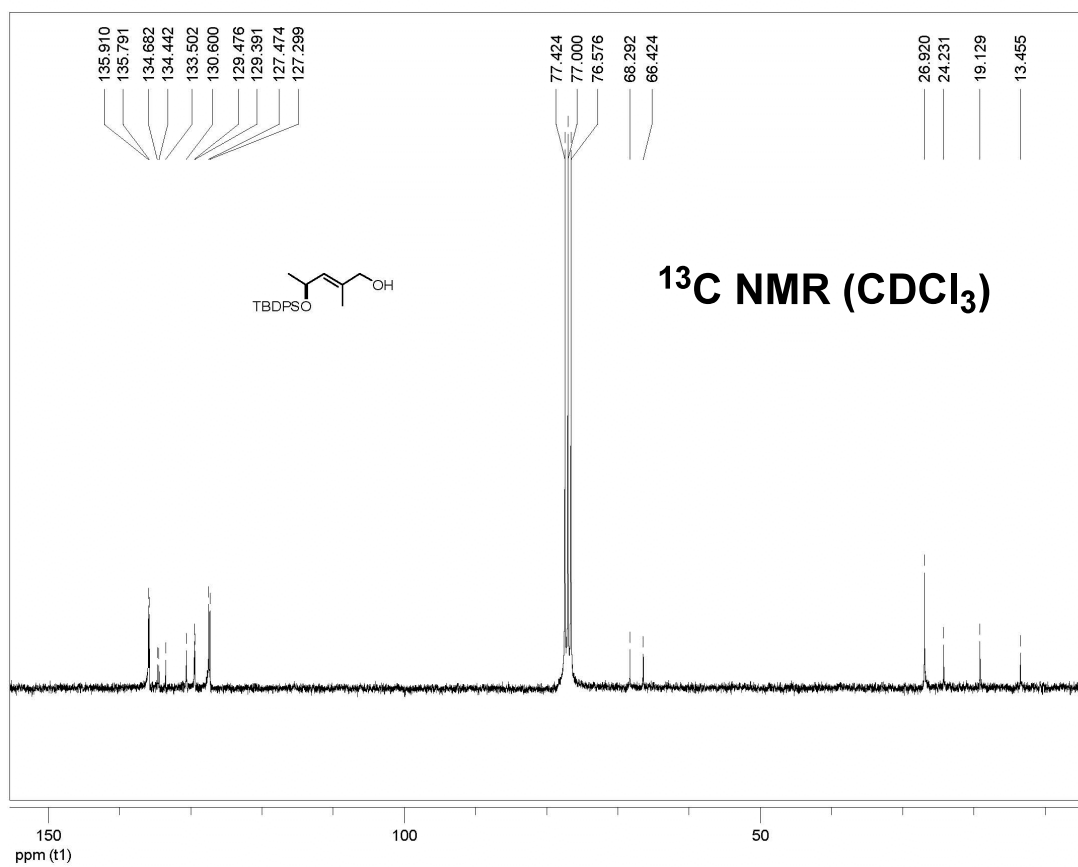
^1H NMR (CDCl_3) ^{13}C NMR (CDCl_3)

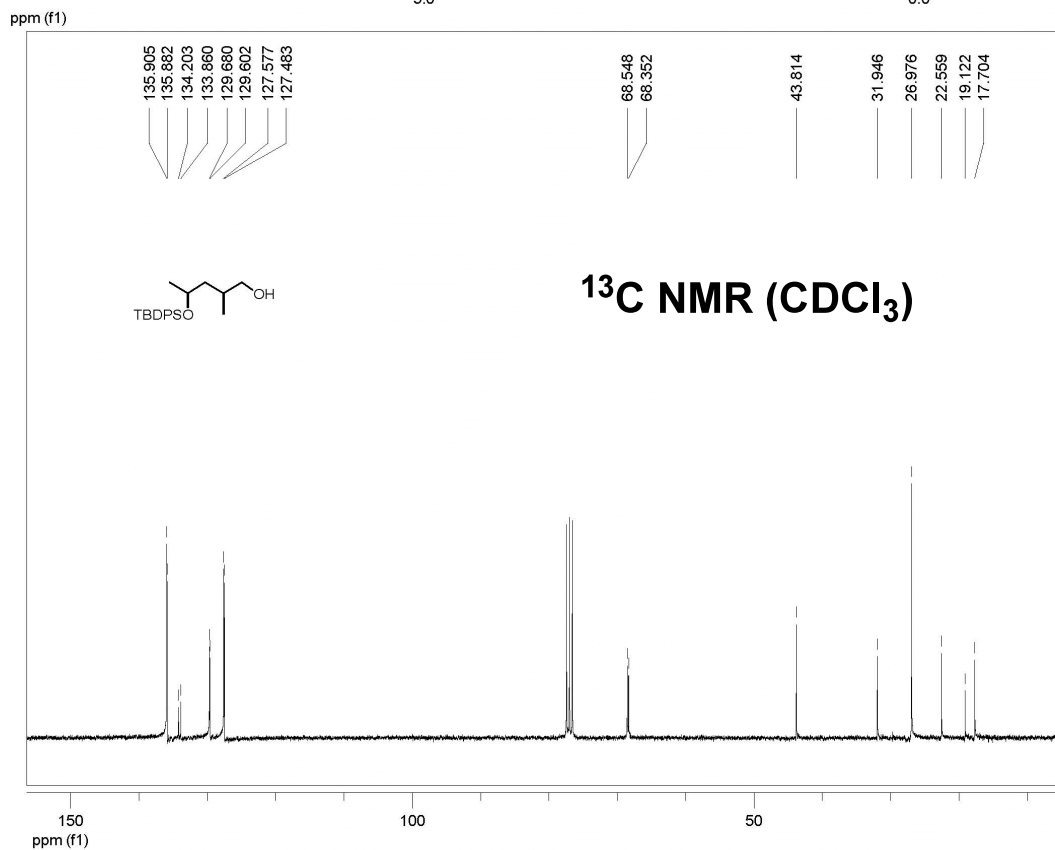


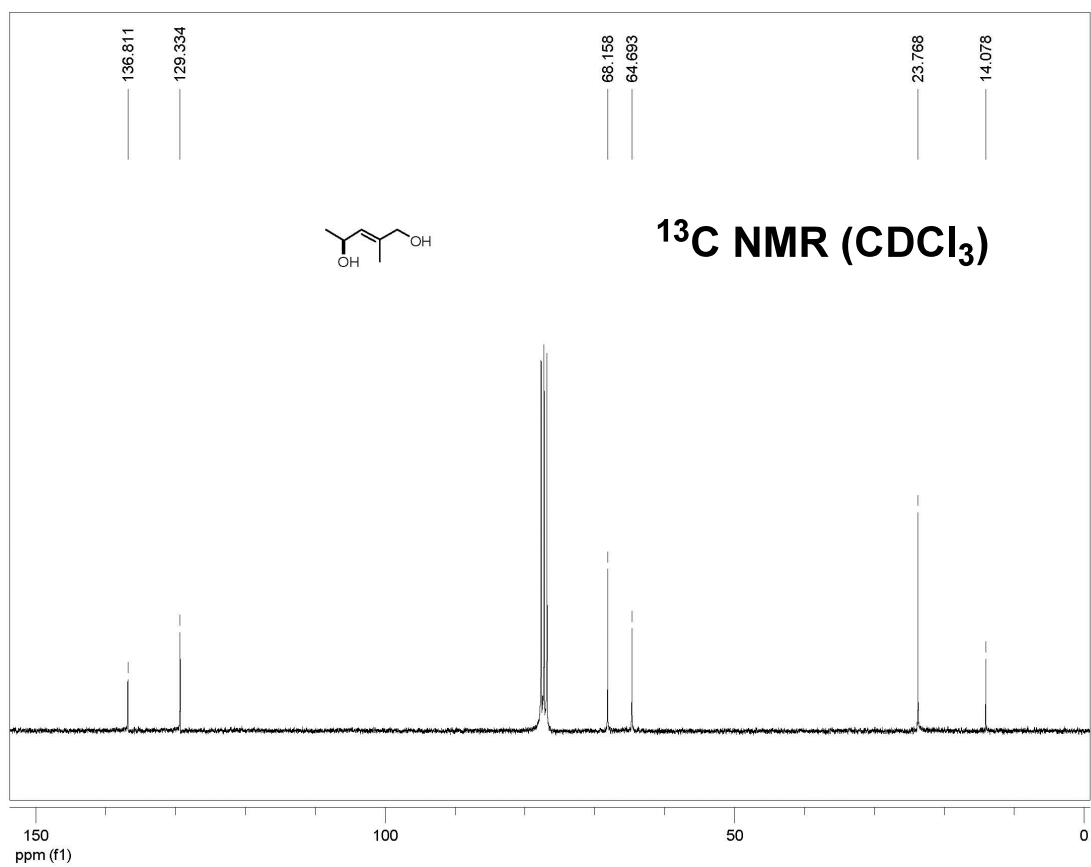
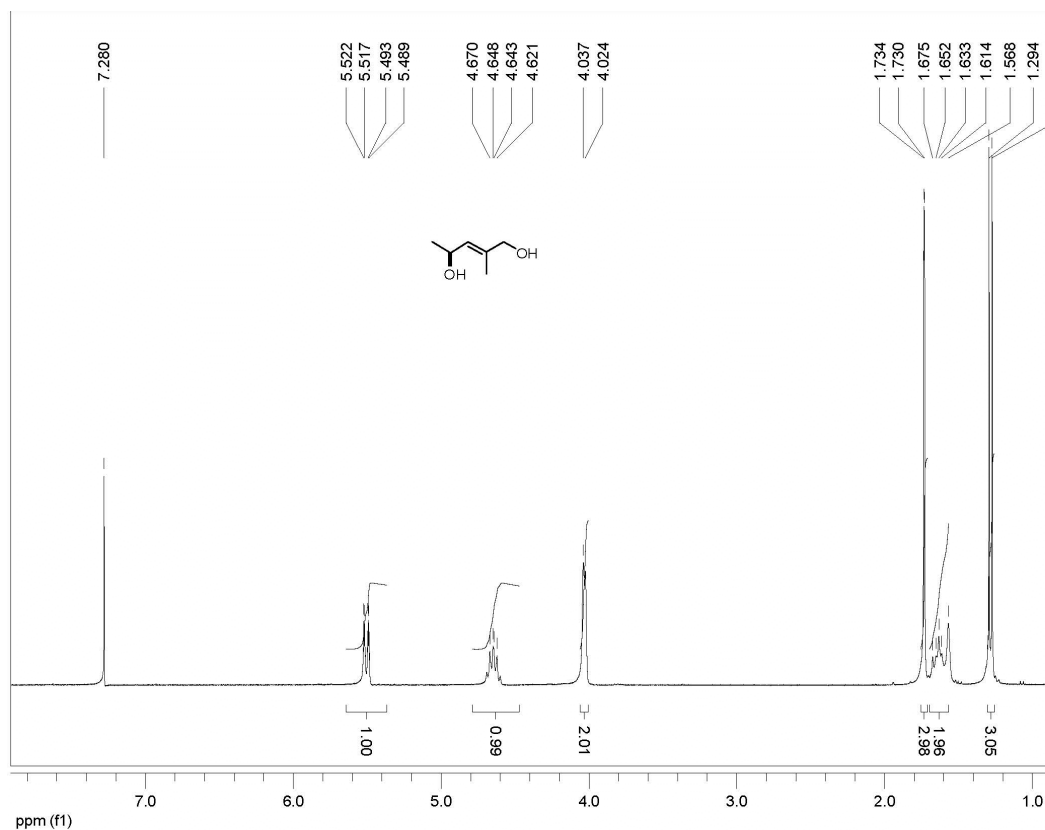


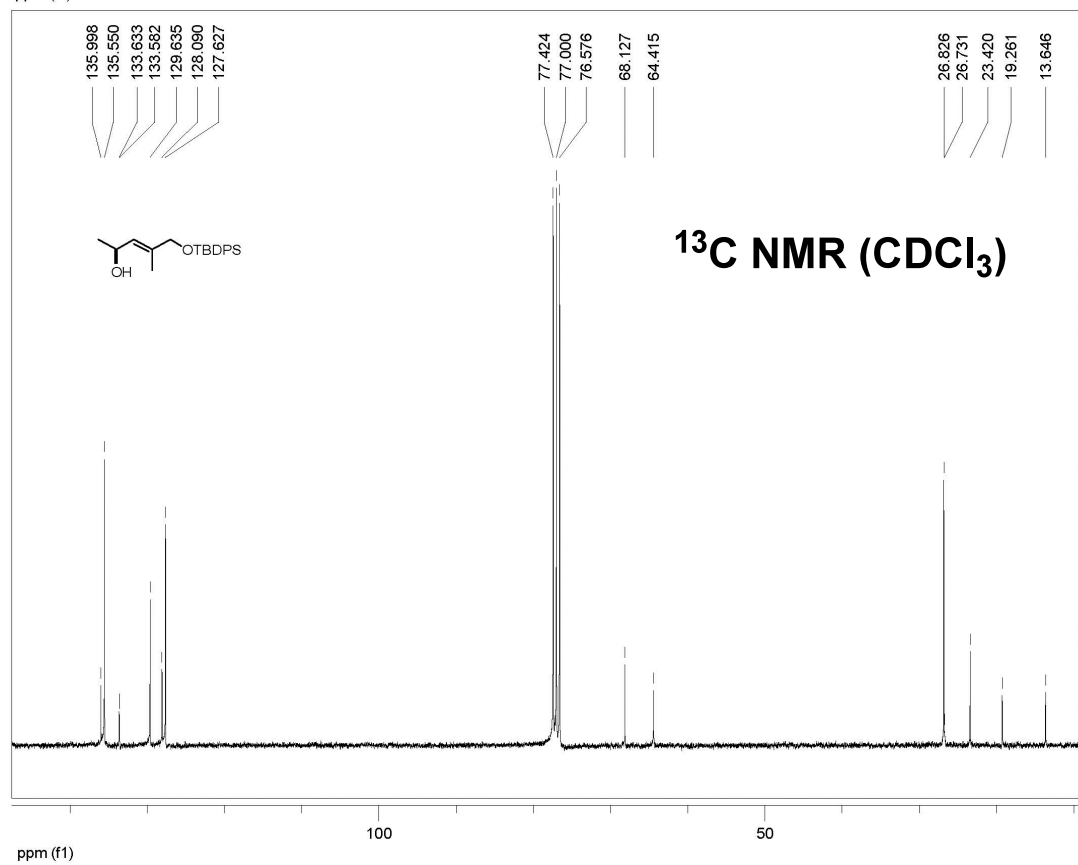
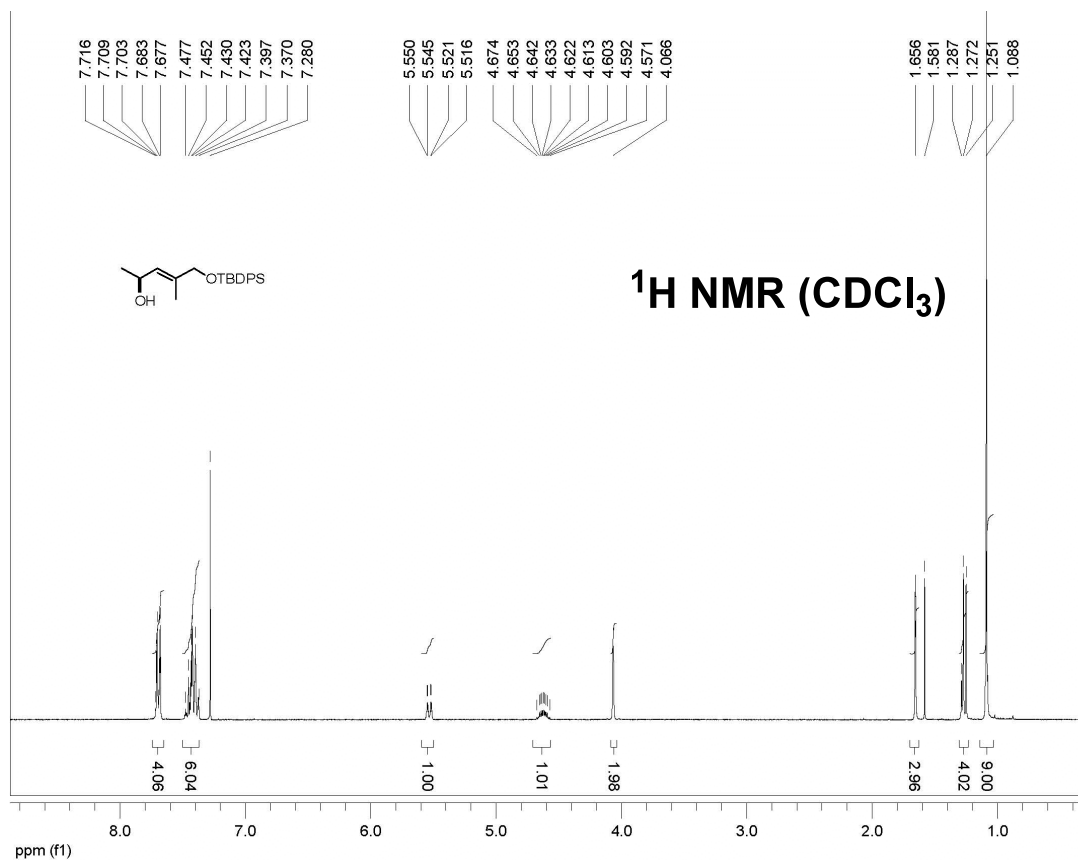


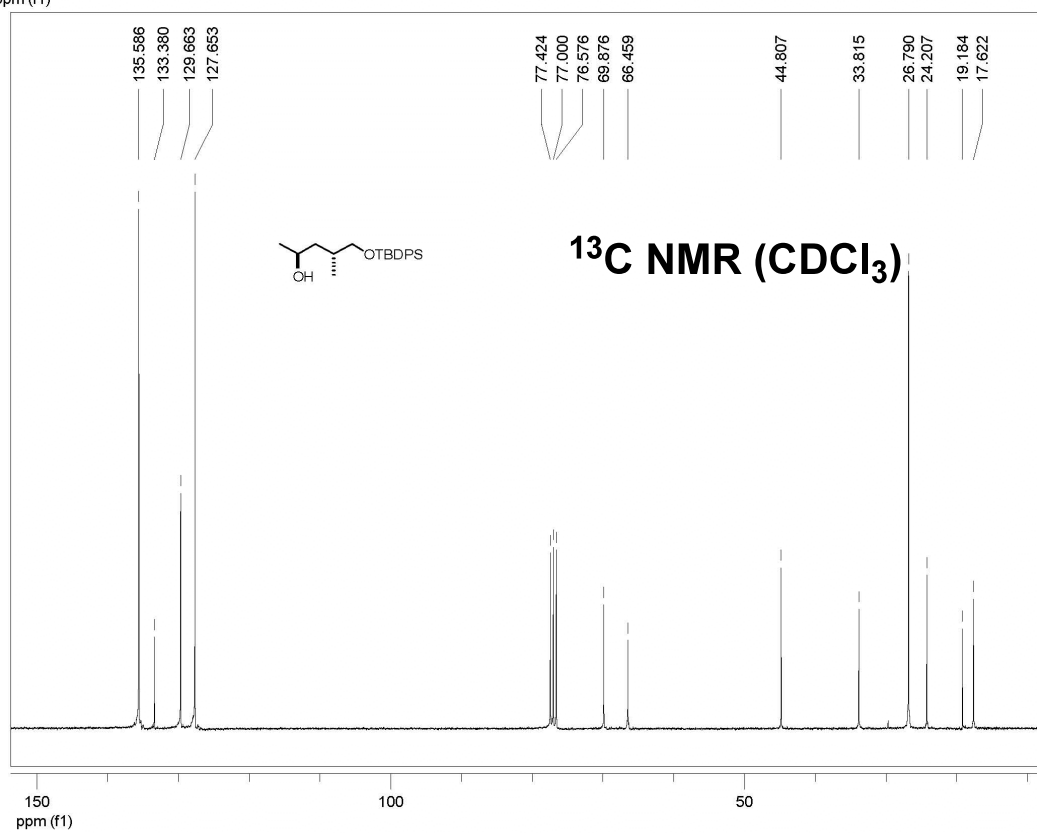


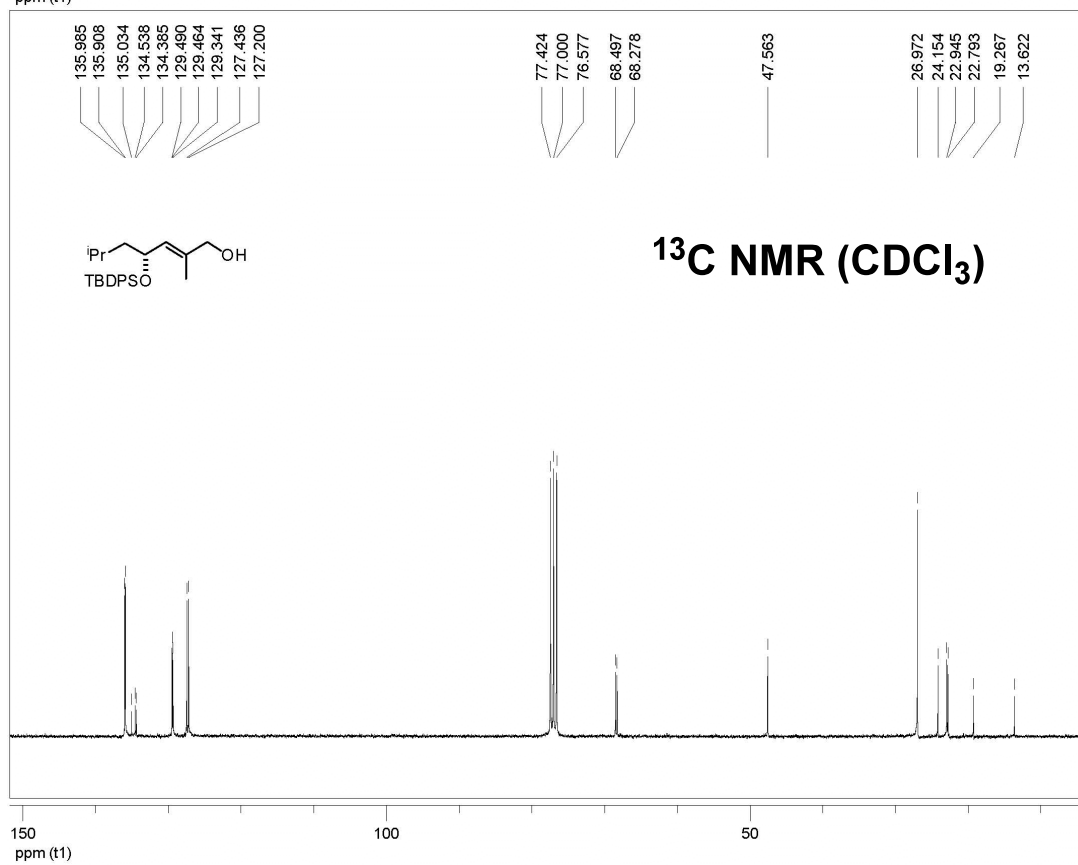
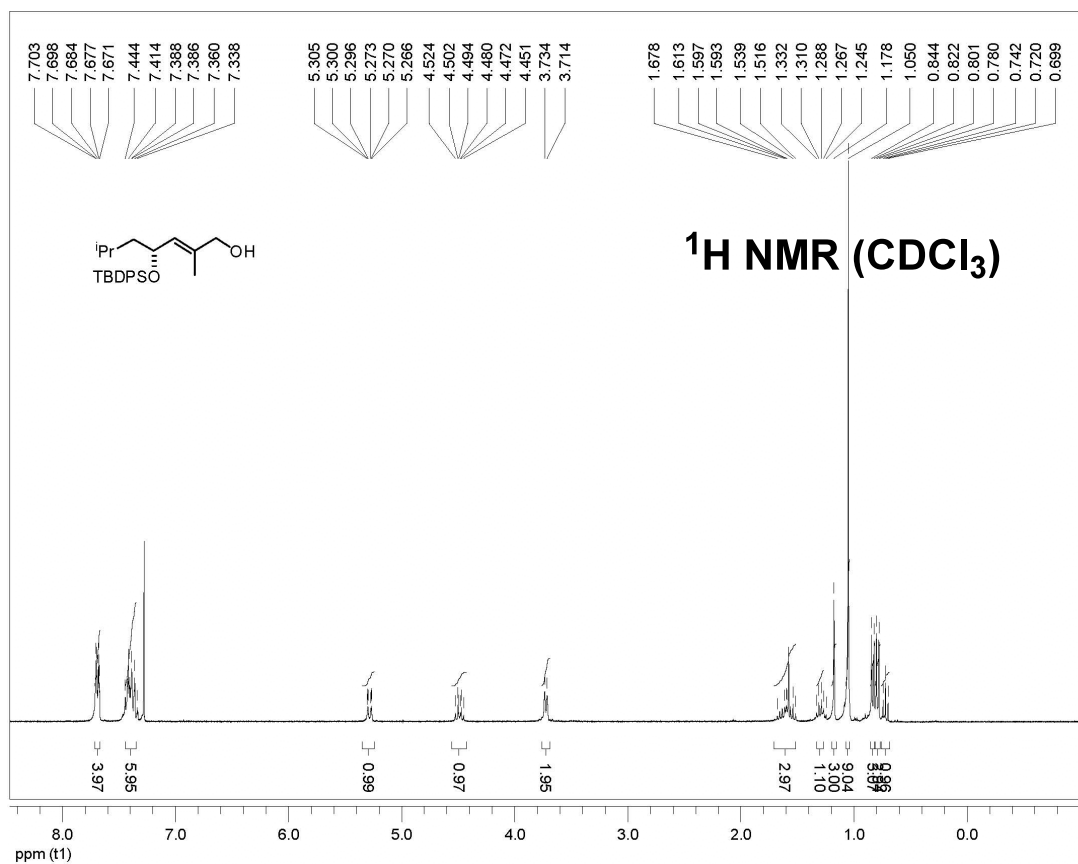


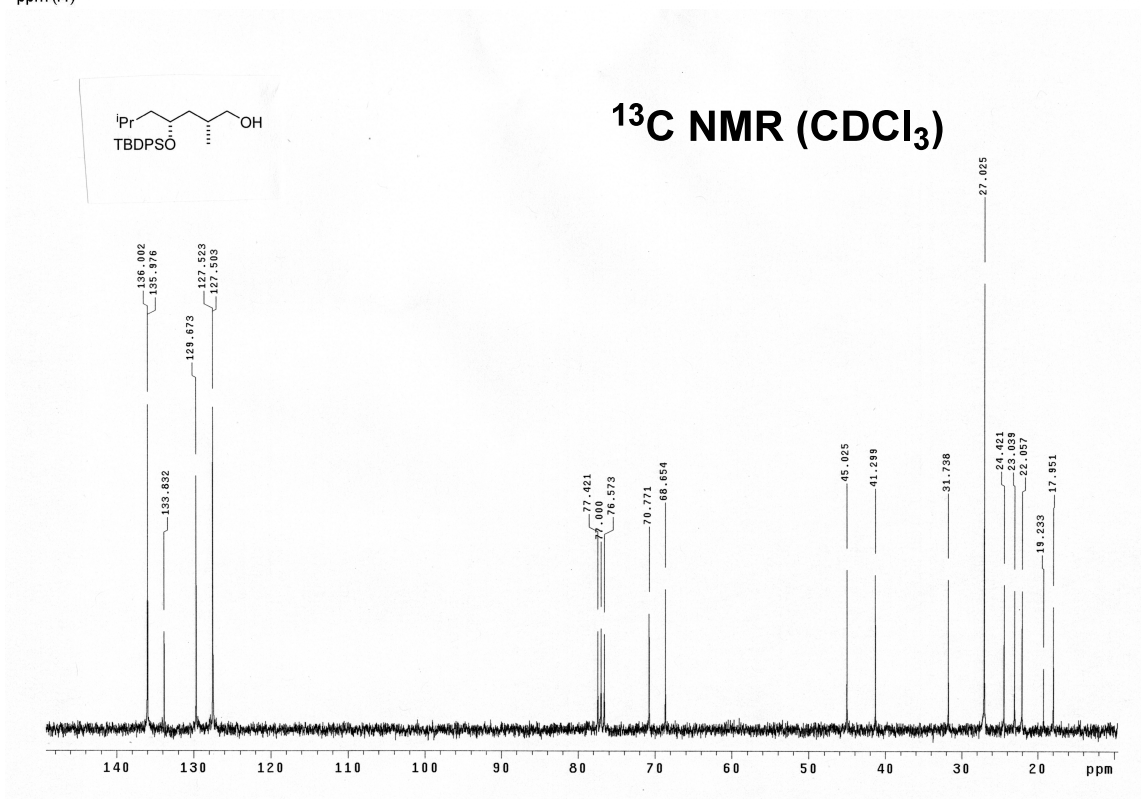
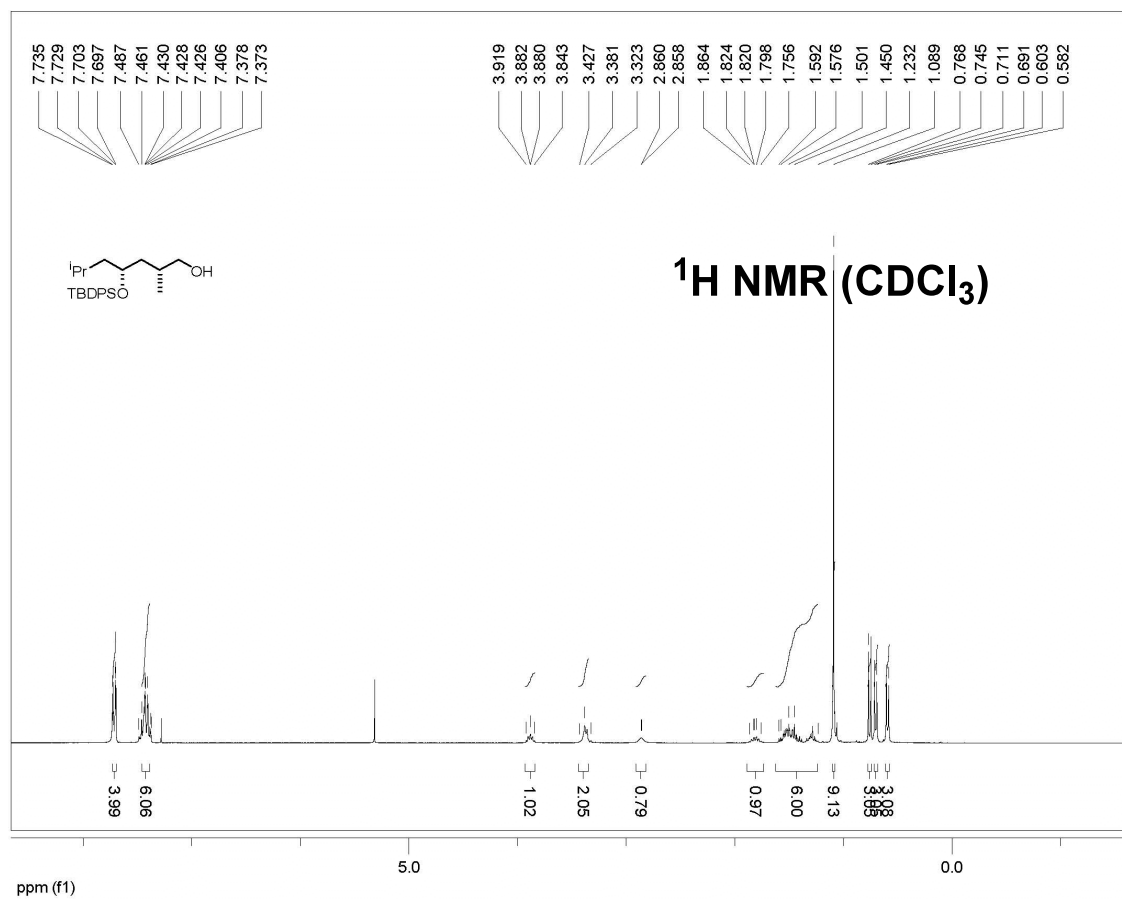


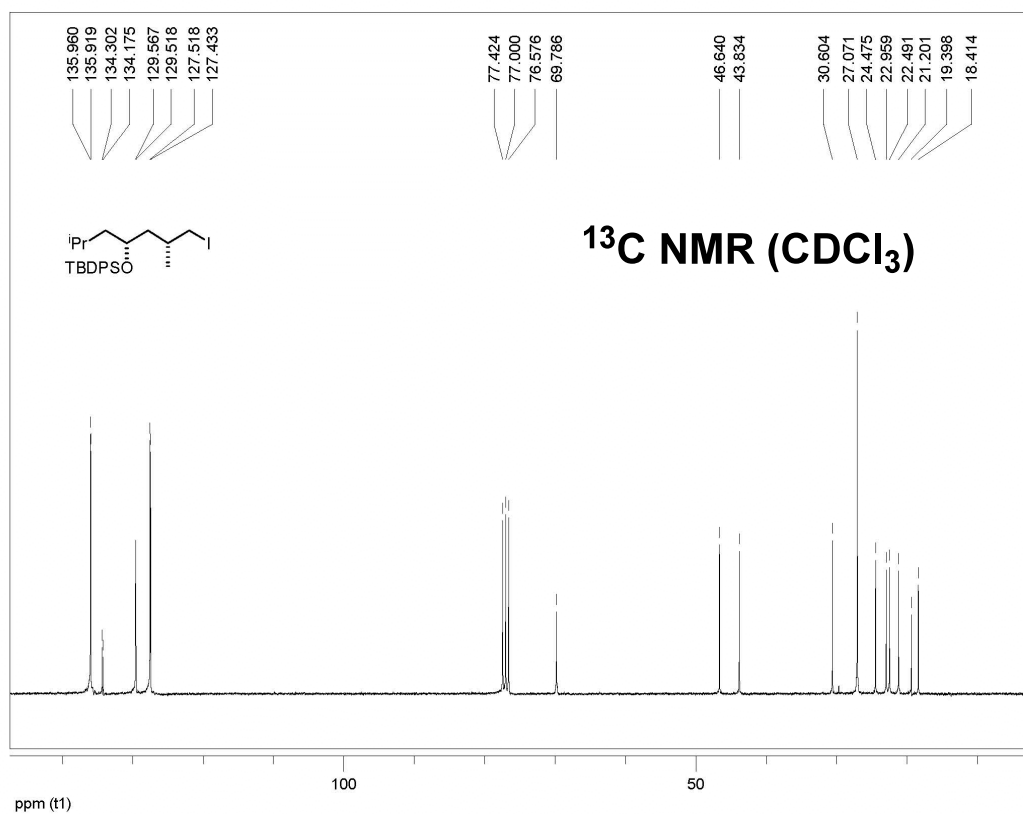
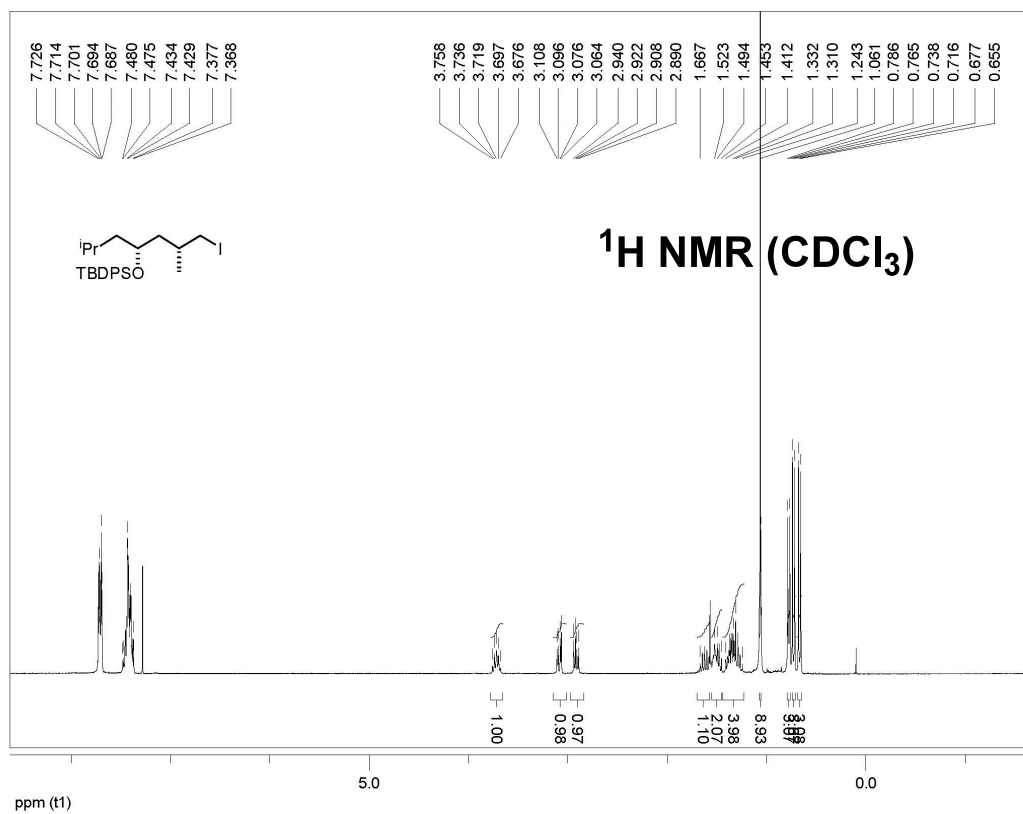


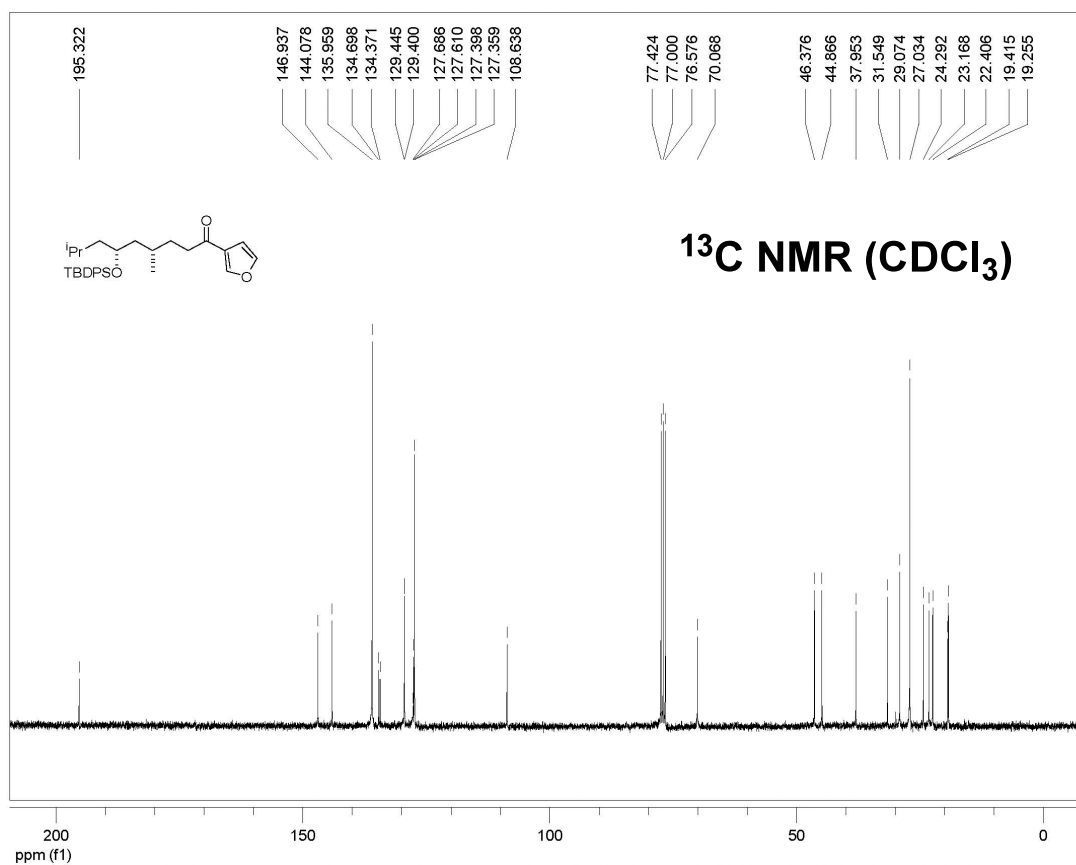
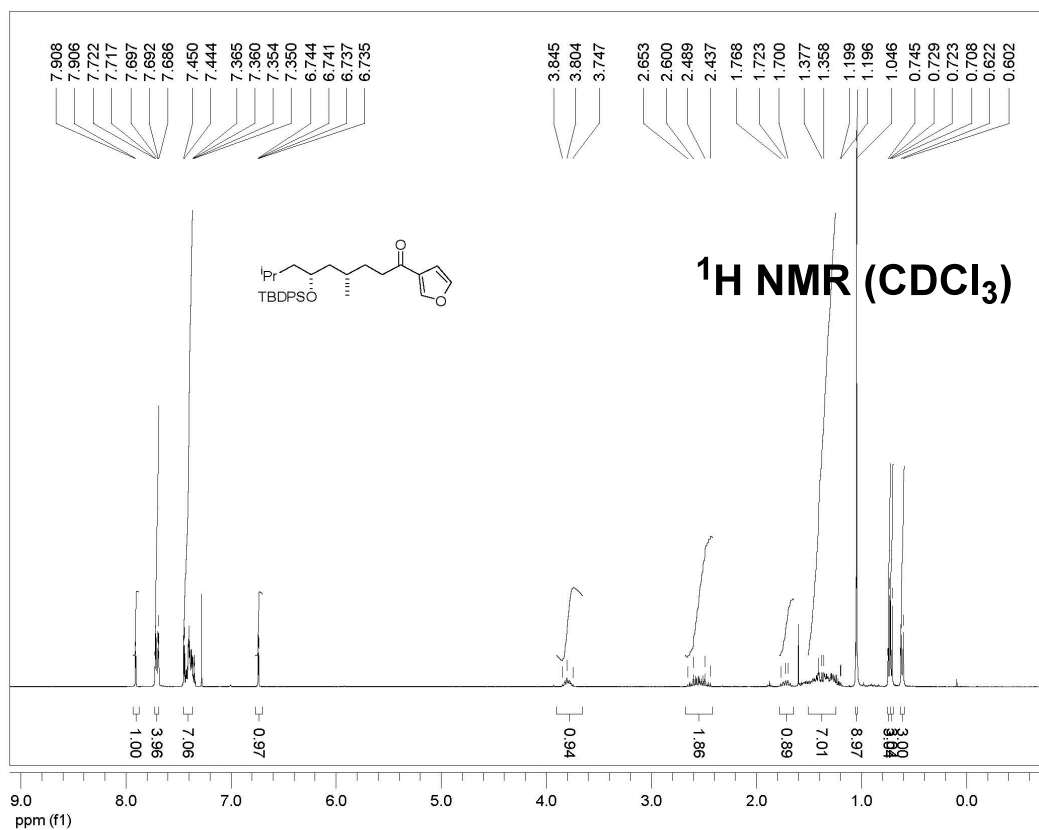


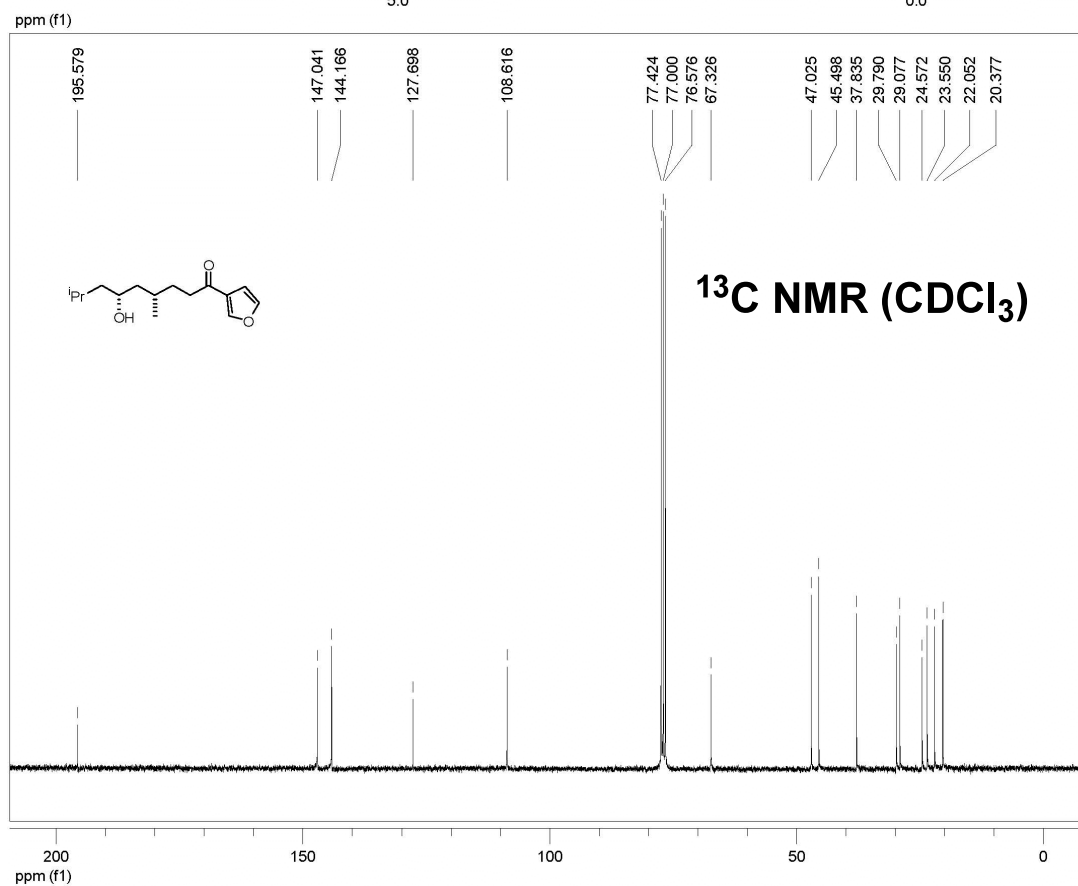
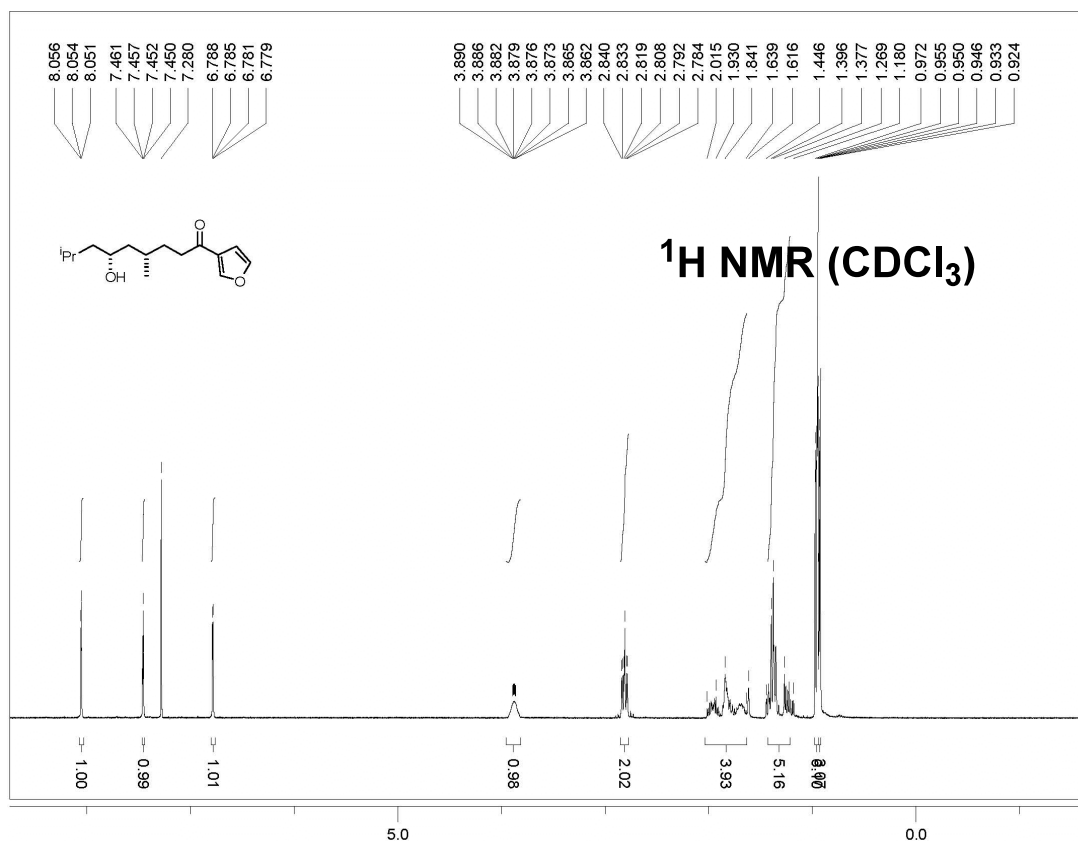






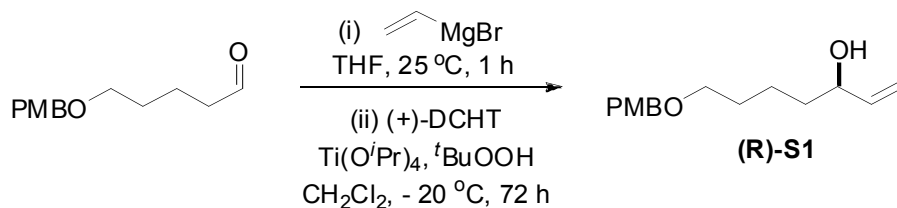






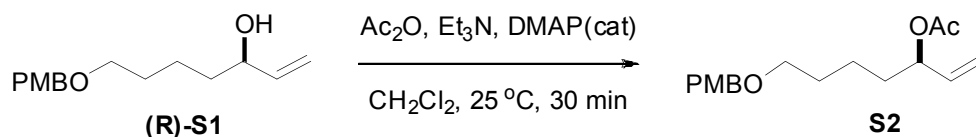
APPENDIX C

EXPERIMENTAL DATA FOR CHAPTER III

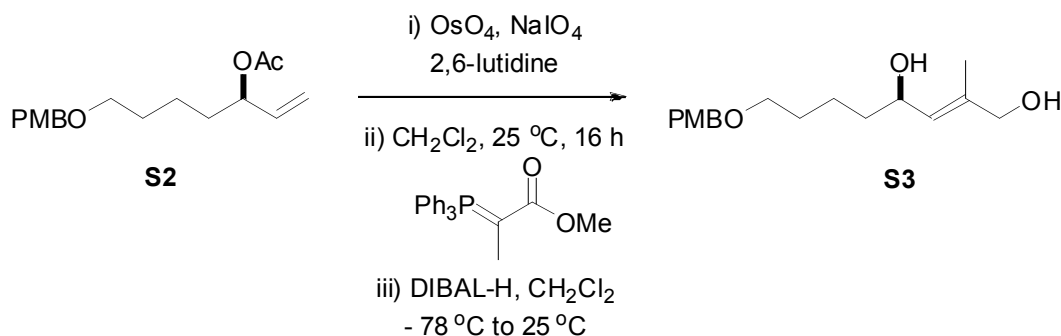


Vinyl magnesium bromide (1M in THF, 142 mL) was added to a round bottom flask and cooled to 0 °C. The known PMB protected aldehyde¹ (10.5 g, 47 mmol) was dissolved in anhydrous THF (50 mL) and added to the previous solution slowly over 1 h. The reaction was stirred at 0 °C for 0.5 h and at 25 °C for 0.5 h, then the reaction was quenched by adding $\text{NH}_4\text{Cl}(\text{s})$ (50 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with brine(s) (20 mL), dried with Na_2SO_4 , and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (30:70) gave racemic alcohol as a colorless oil (10.7 g, 43 mmol, 91%). A 500 ml flask was charged with 4Å molecular sieves (1.2 g, 25% by weight), racemic allylic alcohol (4.75 g, 19mmol) and (+)-DCHT (0.90 g, 2.85 mmol) in CH_2Cl_2 (80 mL). After cooling the mixture to -20 °C, $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.61 mL, 2.09 mmol) was added dropwise via syringe. The reaction mixture was stirred for 30 min at -20 °C followed by addition of $t\text{BuOOH}$ (5.5M in decane, 2.42 mL, 13.3 mmol). The resulting solution was then stirred at -20 °C for 72 h and the reaction was quenched with freshly prepared FeSO_4 -Citric acid aqueous solution (50 mL) at -20 °C.² The mixture was then vigorously stirred at 25 °C for 0.5 h, then the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (30:70) gave allylic alcohol **(R)-S1** as a colorless oil (1.96 g, 7.8 mmol, 46%). The enantiomeric excess was determined >98% *ee* via chiral HPLC. $[\alpha]_D^{21}$ -6.4 (*c* 1.85, CHCl_3); IR (neat) 821, 921, 1035, 1096, 1173, 1247, 1513, 1612, 2859, 2936, 3420(br) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.30-7.25 (m, 2H), 6.92-6.87 (m, 2H), 5.93-5.82 (m, 1H), 5.27-5.10 (m, 2H), 4.45 (s, 2H), 4.15-4.06 (m, 1H), 3.82 (s, 3H), 3.47

(t, $J = 7.5$ Hz, 2H), 1.67-1.43 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 159.3, 141.4, 130.9, 129.5, 114.9, 114.0, 73.4, 72.8, 70.2, 55.5, 37.0, 29.8, 22.3. HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{22}\text{LiO}_3$ $[\text{M}+\text{Li}]^+$ 257.1729. Found 257.1726.

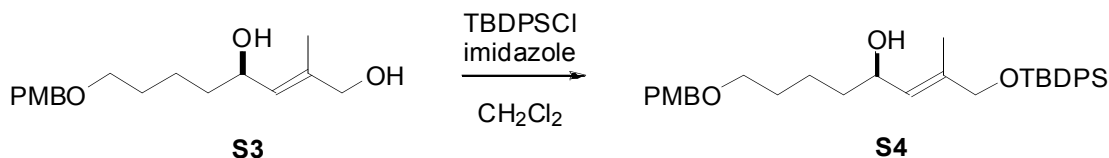


The alcohol **(R)-S1** (2.93 g, 11.7 mmol) and DMAP (61 mg, 0.5 mmol) were dissolved in CH_2Cl_2 (30 mL). Then Ac_2O (1.66 mL, 17.6 mmol) and Et_3N (3.26 mL, 23.4 mmol) were added sequentially. The reaction was stirred at 25 $^\circ\text{C}$ for 30 min, then the reaction was quenched by adding $\text{NH}_4\text{Cl}(\text{s})$ (10 mL). The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (10:90) gave the desired ester **S2** as a colorless oil (3.42 g, 11.7 mmol, 100%). $[\alpha]^{21.4}_{\text{D}} +5.7$ (c 1.40, CHCl_3); IR (neat) 822, 1035, 1099, 1243, 1511, 1612, 1736, 2861, 2940 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.30-7.25 (m, 2H), 6.92-6.87 (m, 2H), 5.84-5.72 (m, 1H), 5.27-5.16 (m, 3H), 4.44 (s, 2H), 3.82 (s, 3H), 3.45 (t, $J = 6.0$ Hz, 2H), 2.07 (s, 3H), 1.69-1.35 (m, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.6, 159.4, 136.7, 130.9, 129.5, 116.9, 114.0, 75.0, 72.8, 70.0, 55.5, 34.2, 29.7, 22.1, 21.5. HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{LiO}_4[\text{M}+\text{Li}]^+$ 299.1835. Found 299.1829.

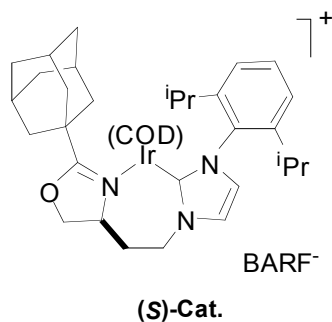
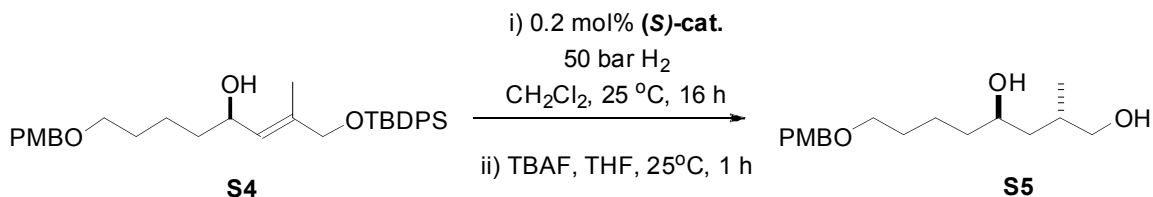


To a solution of **S2** (1.05 g, 3.59 mmol) in Dioxane/ H_2O (36 mL, 3:1) were added 2,6-lutidine (0.83 mL, 7.18 mmol), OsO_4 (2.5 wt. % solution in 2-methyl-2-propanol, 0.90 mL, 0.072 mmol) and NaIO_4 (3.07 g, 14.4 mmol) at 25 °C. The reaction was stirred at 25 °C for 3 h, then water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4 . After concentrated in *vacuo*, the resulting residue was dissolved in CH_2Cl_2 (50 mL) without any further purification and the Wittig reagent (3.1 g, 8.98 mmol) was added in one portion. The reaction was stirred at 25 °C for 16 h, then the solvent was evaporated and the residue was purified by flash chromatography (EtOAc/Hexanes, 20/80). The purified product was dissolved in CH_2Cl_2 (20 mL) and cooled to -78 °C. DIBAL-H (1.0 M in Hexanes, 16.5 mL, 16.5 mmol) was added carefully via syringe pump. The reaction was stirred at -78 °C for 1 h, then allowed to warm to r.t. over 1 h, after which time the reaction was quenched by adding EtOAc (2 mL). The reaction mixture was diluted with CH_2Cl_2 (20 mL) and a saturated aqueous solution of potassium sodium tartrate (10 mL) was added. The resulting mixture was stirred for 1 h and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with EtOAc/hexanes (80:20) to yield the diol **S3** (0.95 g, 90% over three steps) as a colorless oil. $[\alpha]^{21.5}_{\text{D}} -2.0$ (c 0.98, CHCl_3); IR (neat) 819, 1033, 1086, 1173, 1247, 1302, 1442, 1462, 1513, 1612, 2859, 2934, 3366 (br) cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) 7.29-7.25 (m, 2H), 6.92-6.87 (m, 2H), 5.48-5.44 (m, 1H), 4.44-4.39 (m, 3H), 4.04 (s, 2H), 3.82 (s, 3H), 3.46 (d, J = 6.0 Hz, 2H), 1.73 (s, 3H), 1.68-1.37 (m, 8H) (mixed with the peak from H_2O). ^{13}C NMR (75 MHz, CDCl_3) 159.4, 137.8, 130.9, 129.5,

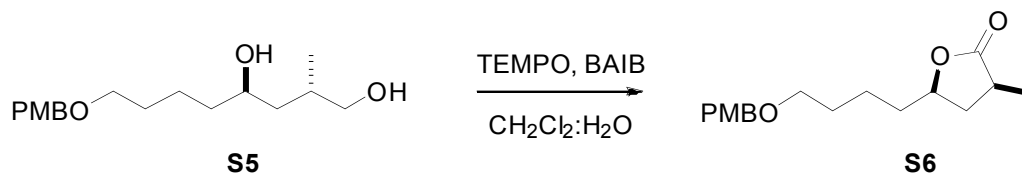
128.2, 114.0, 72.8, 70.1, 68.4, 68.3, 55.5, 37.6, 29.9, 22.3, 14.3. HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{26}\text{LiO}_4[\text{M}+\text{Li}]^+$ 301.1991. Found 301.1999.



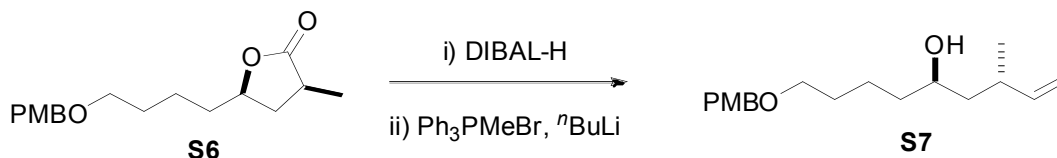
To a solution of compound **S3** (1.15 g, 3.91 mmol) and imidazole (0.29 g, 4.30 mmol) in CH_2Cl_2 (10 mL) was added a solution of TBDPSCI (1.07 g, 3.91 mmol) in CH_2Cl_2 (5 mL, 2 x 1 mL for rinse) dropwise at $-30\text{ }^\circ\text{C}$. The reaction was stirred for 2 h, then quenched with $\text{NaHCO}_3(\text{s})$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 ($3 \times 10\text{ mL}$). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (20:80) gave alcohol **S4** (1.70 g, 81%) as a colorless oil. $[\alpha]_D^{21.6} +4.3$ (c 0.93, CHCl_3); IR (neat) 703, 821, 1036, 1112, 1247, 1427, 1457, 1512, 1611, 2855, 2930, 3070, 3438 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.70-7.68 (m, 4H), 7.43-7.41 (m, 6H), 7.28-7.26 (m, 2H), 6.90-6.87 (m, 2H), 5.51-5.48 (m, 1H), 4.45 (s, 2H), 4.44-4.39 (m, 1H), 4.08 (s, 2H), 3.81 (s, 3H), 1.65-1.28 (m, 10H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, CDCl_3) 159.3, 137.2, 135.8, 133.9(2 peaks), 130.9, 129.9, 129.5, 127.9(2 peaks), 127.2, 114.0, 72.8, 70.3, 68.4(2 peaks), 55.5, 37.5, 29.9, 27.1, 22.3, 19.5, 14.1. HRMS (ESI): Exact mass calcd for $\text{C}_{33}\text{H}_{44}\text{LiO}_4\text{Si}[\text{M}+\text{Li}]^+$ 539.3169. Found 539.3166.



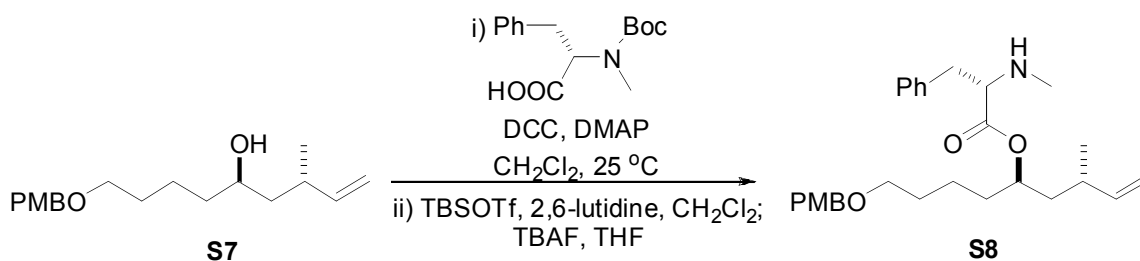
Hydrogenation of **S4** (1.60 g, 3.0 mmol) was carried out according to the general procedure using **(S)-Cat.** (0.2 mol%, 12 mg) in CH₂Cl₂ (3.0 mL). NMR of the crude product showed 100% reduction. HPLC analysis of the crude material showed *anti:syn* ratio to be 61:1.0. After hydrogenation the solvent was evaporated. Then the crude oil was dissolved in THF (5 mL) followed by addition of TBAF (1M in THF, 3.0 mL, 3.0 mmol). The resulting solution was stirred at 25 °C for 1 h, then the reaction was quenched by addition of NH₄Cl(s) (5 mL). The layers were separated, and the aqueous layer was extracted with Et₂O (3 x 5 mL). The organic extract was dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (50:50) gave diol **S5** (0.86 g, 97%) as a colorless oil. $[\alpha]_D^{23} +11.1$ (*c* 0.90, CHCl₃); IR (neat) 820, 1034, 1095, 1173, 1247, 1302, 1461, 1513, 1612, 2860, 2930, 3348 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.26 (m, 2H), 6.92-6.88 (m, 2H), 4.45 (s, 2H), 3.82 (s, 3H), 3.69-3.65 (m, 1 H), 3.58-3.45 (m, 5H), 3.37-3.31 (m, 1H), 1.82-1.38 (m, 9H), 0.90 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 159.3, 130.7, 129.5, 114.0, 72.8, 70.9, 70.2, 68.9, 55.5, 43.4, 38.4, 34.7, 29.8, 22.6, 18.3. HRMS (ESI): Exact mass calcd for C₁₇H₂₈LiO₄[M+Li]⁺ 303.2148. Found 303.2126.



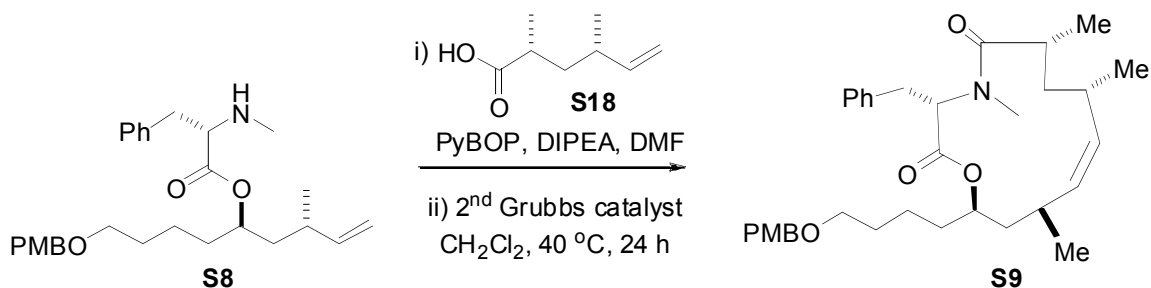
To A solution of diol **S5** (0.80 g, 2.7 mmol) in 15 mL of CH_2Cl_2 and 4.5 mL of H_2O were added TEMPO (42 mg, 0.27 mmol) and $\text{PhI}(\text{OAc})_2$ (1.91 g, 5.94 mmol). The reaction mixture was stirred for 2 h at 25 °C, and then was quenched with saturated aqueous NaHCO_3 , extracted with CH_2Cl_2 , washed with brine, dried over MgSO_4 , and concentrated. Purification by column chromatography (silica gel, 80:20 hexanes-EtOAc) afforded the desired lactone **S6** (0.68 g, 86%) of as a colorless oil; $[\alpha]_D^{23}$ -17.1 (*c* 1.05, CHCl_3); IR (neat) 733, 818, 1034, 1097, 1186, 1247, 1361, 1452, 1514, 1611, 1765, 2849, 2938 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.31-7.26 (m, 2H), 6.93-6.88 (m, 2H), 4.45 (s, 2H), 4.39-4.30 (m, 1 H), 3.83 (s, 3H), 3.48 (t, J = 6.0 Hz, 2H), 2.70-2.64 (m, 1H), 2.54-2.45 (m, 1H), 1.84-1.46 (m, 6H), 1.29 (d, J = 6.0 Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) 179.8, 159.4, 130.8, 129.5, 114.0, 78.8, 72.8, 69.9, 55.5, 37.6, 36.2, 35.5, 29.7, 22.4, 15.4. HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{24}\text{LiO}_4[\text{M}+\text{Li}]^+$ 299.1835. Found 299.1820.



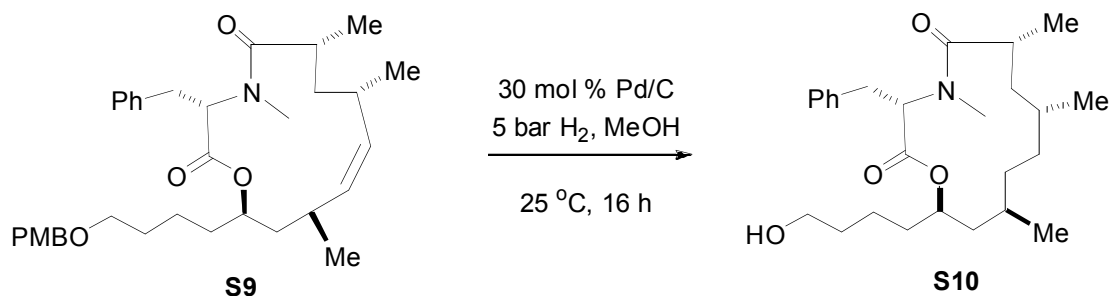
To a solution of lactone **S6** (427 mg, 1.50 mmol) in CH_2Cl_2 (10 mL) under nitrogen was added DIBAL-H (1M in CH_2Cl_2 , 3.0 mL, 3.0 mmol) at -78°C . The reaction mixture was stirred at -78°C for 1 h, and then was quenched with 1 mL of EtOAc. The mixture was diluted with CH_2Cl_2 (20 mL) and saturated potassium sodium tartrate aqueous solution (10 mL) was added. The resulting solution was stirred for 1 h at 25°C and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was directly used in the next step. To a solution of 2.68 g (7.5 mmol) of methyl triphenyl phosphonium bromide in 30 mL of THF under nitrogen was added 2.94 mL (7.35 mmol) of 2.5 M solution of *n*-BuLi in hexanes at 0°C . The solution was stirred at 0°C for 30 min, and then the crude lactol in 10 mL of THF was added. The reaction was stirred at 0°C for 3 h, and then the reaction mixture was quenched with saturated aqueous NH_4Cl , extracted with ether, washed with brine, dried over MgSO_4 , and concentrated. Purification by column chromatography (silica gel, 85/15 hexanes-EtOAc) gave 322 mg (76%) of alcohol **S7** as a colorless oil; $[\alpha]_D^{20} -4.1$ (*c* 0.96, CHCl_3); IR (neat) 814, 909, 1035, 1097, 1172, 1247, 1302, 1453, 1514, 1613, 2861, 2932, 3070, 3430 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.29-7.26 (m, 2H), 6.92-6.88 (m, 2H), 5.85-5.73 (m, 1H), 5.07-4.94 (m, 2H), 4.45 (s, 2H), 3.82 (s, 3H), 3.74-3.66 (m, 1H), 3.47 (t, *J* = 7.5 Hz, 2H), 2.39-2.29 (m, 1H), 1.61-1.40 (m, 8H), 1.03 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.6, 135.5, 134.1, 130.1, 129.4, 127.5, 69.4, 41.2, 33.6, 29.1, 26.8, 22.2, 20.8, 19.3, 16.6, 14.6. HRMS (ESI): Exact mass calcd for $\text{C}_{18}\text{H}_{29}\text{O}_3[\text{M}+\text{H}]^+$ 293.2117. Found 293.2119.



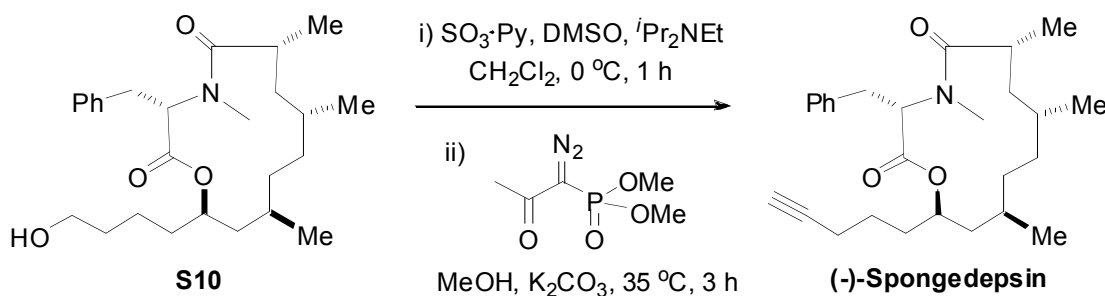
To a solution of (*S*)-*N*-Boc-methylphenylalanine (461 mg, 1.65 mmol), allylic alcohol **S7** (322 mg, 1.1 mmol) and DMAP (27 mg, 0.22 mmol) in 5 mL of CH_2Cl_2 was added a solution of DCC (454 mg, 2.2 mmol) in 5 mL of CH_2Cl_2 . The reaction mixture was stirred overnight, and then filtered on a pad of celite and washed with ether. The residue was concentrated and purified by column chromatography (silica gel, 90:10 hexanes-EtOAc) to give 609 mg (100%) of the coupled product as a colorless oil. To a solution of the previous coupling product (609 mg, 1.1 mmol) in CH_2Cl_2 (15 mL) were added 2,6-lutidine (0.38 mL, 3.3 mmol) and *tert*-butyldimethylsilyl trifluoromethane sulfonate (0.63 mL, 2.75 mmol) at 25 °C. The resulting reaction mixture was allowed to stir for 1.5 h before saturated aqueous NH_4Cl solution (10 mL) was added. The aqueous mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was redissolved in THF (10 mL) and treated with tetra-*n*-butylammonium fluoride (1.0 M in THF, 1.3 mL, 1.3 mmol). The reaction mixture was allowed to stir at rt for 1 h before saturated aqueous NH_4Cl solution (10 mL) was added. The aqueous mixture was extracted with ethyl acetate (4 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 70:30) of the resulting residue gave amine **S8** (480 mg, 96% for 2 steps) as a colorless oil; $[\alpha]^{20.3}_{\text{D}} +10.3$ (*c* 0.58, CHCl_3); IR (neat) 700, 1036, 1098, 1179, 1247, 1453, 1511, 1611, 1726, 2850, 2929, 3325 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.28-7.20 (m, 7H), 6.89-6.87 (m, 2H), 5.78-5.66 (m, 1H), 4.99-4.89 (m, 3H), 4.43 (s, 2H), 3.81 (s, 3H), 3.45-3.37 (m, 3H), 2.94 (d, *J* = 9.0 Hz, 2H), 2.37 (s, 3H), 2.16-2.09 (m, 1H), 1.59-1.18 (m, 9H), 0.99 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.3, 159.1, 143.9, 137.3, 130.6, 129.2(2 peaks), 128.4, 126.7, 113.7, 112.8, 73.0, 72.6, 69.7, 64.8, 55.3, 40.5, 39.6, 34.8, 34.3, 33.8, 29.6, 21.6, 19.9. HRMS (ESI): calcd for $\text{C}_{28}\text{H}_{40}\text{NO}_4$ $[\text{M}+\text{H}]^+$ 454.2957. Found 454.2962.



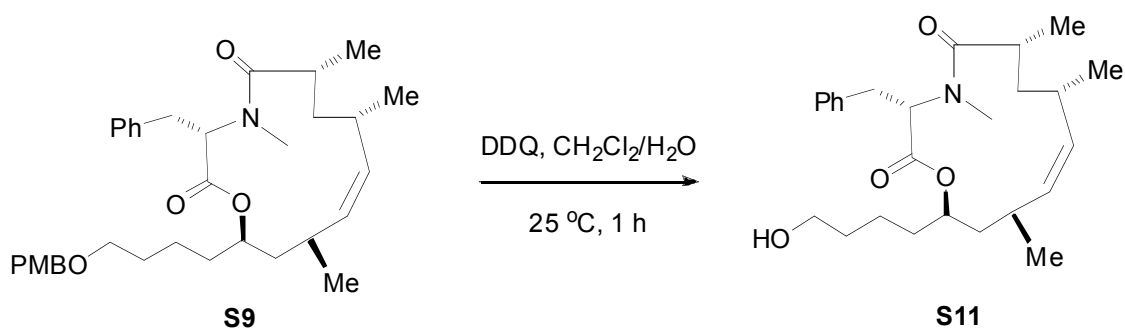
To a solution of dimethyl acid **S18** (87 mg, 0.61 mmol) in DMF (9 mL) were added di-*iso*-propylethyl amine (0.32 mL, 1.84 mmol) and PyBOP (345 mg, 0.66 mmol). The resulting mixture was allowed to stir at rt for 2 min before amine **S8** (230 mg, 0.51 mmol) in DMF (9 mL) were added. The reaction mixture was stirred at rt for 24 h before it was partitioned between ethyl ether (50 mL) and saturated aqueous NaHCO₃ solution (10 mL). The organic layer was washed with brine (10 mL). The combined aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. Silica gel column chromatography (hexanes-ethyl acetate, 85:15) of the resulting residue gave amides as a mixture of rotamers (0.27 g, 0.47 mmol, 92%). To a solution of 170 mg (0.29 mmol) of previous amide in 500 mL of dry CH₂Cl₂ under argon was added 25 mg (0.028 mmol) of 2nd generation Grubbs catalyst. After stirring overnight at 40 °C, 13 mg (0.014 mmol) of 2nd generation Grubbs catalyst was added. The solution was stirred for additional 8 h at reflux, and the reaction mixture was concentrated and purified by column chromatography (silica gel, 80/20 hexanes-EtOAc) to afford 140 mg (90%) of desired product **S9** as a colorless oil. $[\alpha]_D^{20}$ -96.5 (*c* 0.29, CHCl₃); IR (neat) 1099, 1171, 1220, 1247, 1459, 1507, 1641, 1727, 2848, 2921, 2956 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.32-7.16 (m, 7H), 6.91-6.88 (m, 2H), 5.23-5.13 (m, 2H), 5.08-5.04 (m, 1H), 4.44 (s, 2H), 3.82 (s, 3H), 3.62-3.59 (m, 1H), 3.51-3.44 (m, 3H), 3.37-3.33 (m, 1H), 2.80-2.74 (m, 1H), 2.66 (s, 3H), 2.50-2.44 (m, 1H), 2.16-2.09 (m, 1H), 1.92-1.87 (m, 1H), 1.65-1.27 (m, 8H), 1.18-1.15 (m, 1H), 1.12 (d, *J* = 10.0 Hz, 3H), 1.00 (d, *J* = 10.0 Hz, 3H), 0.99 (d, *J* = 5.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 176.8, 170.3, 159.3, 139.0, 136.4, 135.9, 130.9, 129.7, 129.5, 128.7, 126.7, 114.0, 73.5, 72.8, 70.0, 67.2, 55.5, 44.5, 43.3, 39.7, 35.5, 34.7, 33.9, 30.4, 30.0, 27.1, 22.2, 20.2, 19.7, 18.9. HRMS (ESI): Exact mass calcd for C₃₄H₄₈NO₅[M+H]⁺ 550.3532. Found 550.3529.



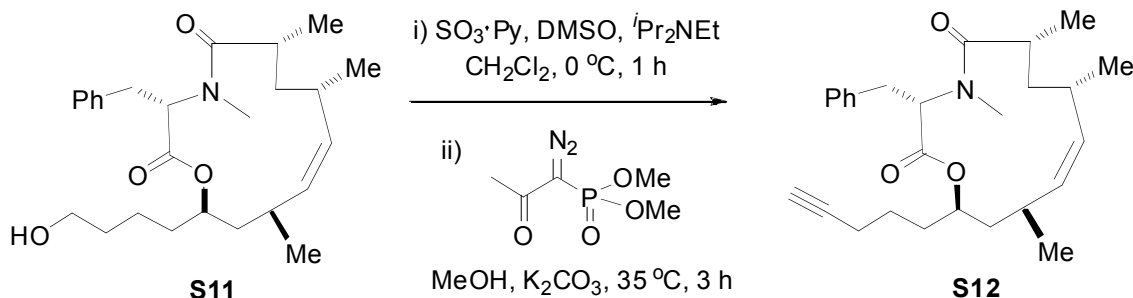
The solution of 99 mg (0.18 mmol) of the macrocyclic olefin **S9** and 60 mg (0.06 mmol) of 10% Pd/C in 6 mL of MeOH was putted in to a hydrogenation bomb. The hydrogen pressure was raised to 5 bar and the reaction was stirred for 16 h. The mixture was filtered on a plug of silica gel (5 cm), washed with MeOH, and concentrated to give 67 mg (86%) of free saturated alcohol **S10** as a colorless oil. $[\alpha]^{19.6}_{\text{D}} -168$ (c 1.01, CHCl_3); IR (neat) 702, 752, 1079, 1173, 1212, 1276, 1456, 1634, 1738, 2853, 2922, 2956, 3431 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.31-7.17 (m, 5H), 5.19-5.14 (m, 1H), 3.68-3.49 (m, 4H), 3.34-3.30 (m, 1H), 2.84-2.78 (m, 1H), 2.66 (s, 3H), 2.01 (t, $J = 10.0$ Hz, 1H), 1.71-1.31 (m, 12H), 1.13 (d, $J = 10.0$ Hz, 3H), 1.10-1.01 (m, 2H), 0.91-0.86 (m, 6H), 0.78-0.76 (m, 1H), 0.75-0.73 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 177.0, 170.4, 139.0, 129.7, 128.7, 126.7, 73.4, 67.2, 63.0, 39.9, 39.4, 37.3, 35.9, 34.7, 33.6, 32.9, 32.6, 31.7, 27.5, 24.3, 22.5, 21.9, 21.6, 19.0. HRMS (ESI): Exact mass calcd for $\text{C}_{26}\text{H}_{42}\text{NO}_4[\text{M}+\text{H}]^+$ 432.3114. Found 432.3117.



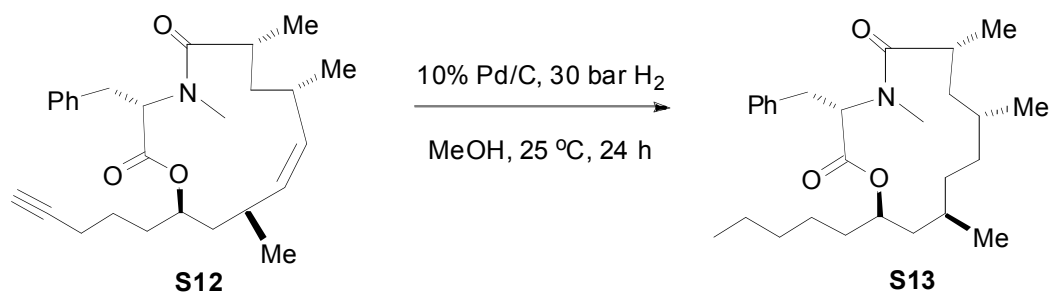
The alcohol **S10** (40 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (2 mL) at 0 °C. DMSO (0.16 mL, 2.25 mmol) and DIPEA (0.16 mL, 0.90 mmol) were added. To this solution at 0 °C, $\text{SO}_3\cdot\text{Py}$ complex (72 mg, 0.45 mmol) was added and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched with saturated aqueous NH_4Cl (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde was purified through column chromatography, eluting with EtOAc/hexanes (20:80) to give desired aldehyde (39.3 mg, 100%) as a colorless solid. To a solution of the aldehyde prepared above and 225 mg (1.17 mmol) of Ohira-Bestmann's reagent³ in 20 mL of MeOH was added 143 mg (1.04 mmol) of K_2CO_3 under nitrogen. The solution was stirred for 3 h at 35 °C, and then the reaction mixture was quenched with saturated aqueous NH_4Cl , extracted with ether, dried over MgSO_4 , and concentrated. Purification by column chromatography (silica gel, 95/5 hexanes-EtOAc) gave 32.6 mg (87%, 2 steps) of (–)-spongidepsin as a crystalline solid; $[\alpha]_D^{21}$ -152 (*c* 0.25, MeOH); $[\alpha]_D^{23}$ -203.2 (*c* 0.4, MeOH)⁴; IR (neat) 701, 754, 1070, 1172, 1209, 1275, 1456, 1636, 1731, 2110, 2850, 2870, 2930, 2959, 3303 cm^{-1} ; ^1H NMR (500 MHz, CD_3OD) δ 7.34–7.17 (m, 5H), 5.20–5.13 (m, 1H), 4.02–3.98 (m, 1H), 3.46–3.23 (m, 3H), 2.99–2.91 (m, 1H), 2.72 (s, 3H), 2.25–2.21 (m, 3H), 1.94–1.89 (m, 1H), 1.72–1.41 (m, 9H), 1.08 (d, $J=7$ Hz, 3H), 1.07 (m, 1H), 1.06 (m, 1H), 0.93 (d, $J=7$ Hz, 3H), 0.91 (m, 1H), 0.90 (d, $J=7$ Hz, 3H), 0.79 (ddd, $J=3, 11.5, 14$ Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 179.6, 172.1, 139.7, 130.8, 129.7, 127.9, 84.8, 74.2, 70.1, 67.8, 40.6, 40.5, 38.2, 36.0, 35.5, 34.7, 33.6, 32.7, 28.5, 25.7, 25.4, 22.6, 21.8, 19.1(2 peaks); HRMS (ESI): Exact mass calcd for $\text{C}_{27}\text{H}_{40}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 426.3008, found: 426.3012.



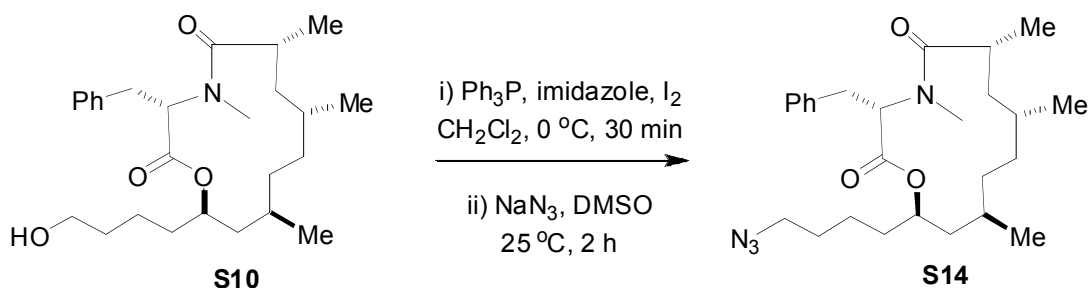
The macrocyclic olefin **S9** (140 mg, 0.26 mmol) was dissolved in $\text{CH}_2\text{Cl}_2\text{-H}_2\text{O}$ (2 mL, 19:1.0) and DDQ (86 mg, 0.39 mmol) was added in one portion. The solution was stirred at 25 °C for 1 h, then the reaction was quenched by adding $\text{NaHCO}_3(s)$ (2 mL). The mixture was diluted with CH_2Cl_2 (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (5 mL x 3). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, 70/30 hexanes-EtOAc) gave 99.1 mg (0.23 mmol, 89%) of alcohol **S11** as a crystalline solid $[\alpha]_D^{20.7} -157.8$ (c 0.38, CHCl_3); IR (neat) 702, 1078, 1173, 1220, 1277, 1413, 1455, 1630, 1729, 2871, 2930, 2958, 3419 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.33-7.18 (m, 5H), 5.23-5.06 (m, 3H), 3.67-3.61 (m, 3H), 3.51-3.46 (m, 1H), 3.38-3.34 (m, 1H), 2.81-2.75 (m, 1H), 2.68 (s, 3H), 2.50-2.45 (m, 1H), 2.14-2.11 (m, 1H), 1.90 (t, $J = 15.0$ Hz, 1H), 1.65-1.14 (m, 10H), 1.12 (d, $J = 10.0$ Hz, 3H), 1.01 (d, $J = 10.0$ Hz, 3H), 1.00 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.9, 170.5, 138.9, 136.3, 135.9, 129.7, 128.7, 126.8, 73.4, 67.2, 63.0, 44.5, 43.3, 39.7, 35.5, 34.7, 33.9, 32.8, 30.4, 27.1, 21.8, 20.2, 19.7, 18.9. HRMS (ESI): Exact mass calcd for $\text{C}_{26}\text{H}_{40}\text{NO}_4[\text{M}+\text{H}]^+$ 430.2957. Found 430.2952.



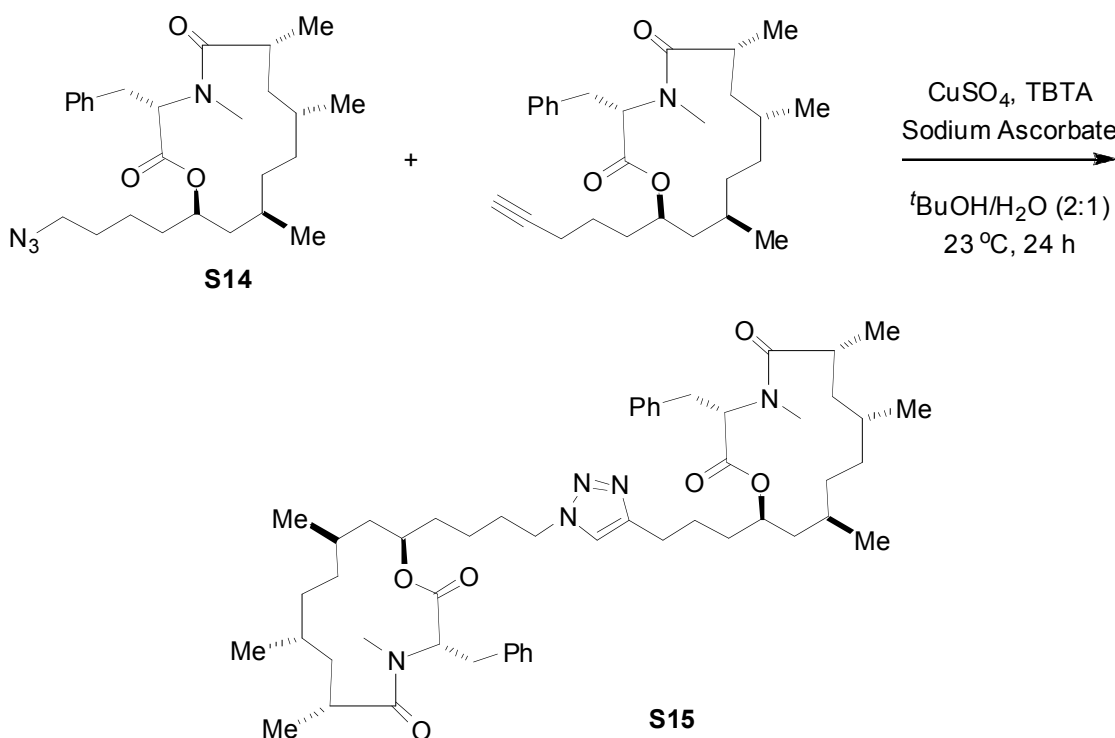
The alcohol **S11** (42.7 mg, 0.10 mmol) was dissolved in CH_2Cl_2 (2 mL) at 0 °C. DMSO (0.18 mL, 2.5 mmol) and DIPEA (0.18 mL, 1.0 mmol) were added. To this solution at 0 °C, $\text{SO}_3\cdot\text{Py}$ complex (80 mg, 0.50 mmol) was added and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched with NH_4Cl (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 mL x 3). The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde was purified through column chromatography, eluting with EtOAc/hexanes (20:80) to give desired aldehyde (42 mg, 100%) as colorless solid. To a solution of the aldehyde prepared above and 0.25 g (1.3 mmol) of Ohira-Bestmann's reagent⁴ in 20 mL of MeOH was added 159 mg (1.15 mmol) of K_2CO_3 under nitrogen. After stirring for 3 h at 25 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl , extracted with ether, dried over MgSO_4 , and concentrated. Purification by column chromatography (silica gel, 95/5 hexanes-EtOAc) gave 37.6 mg (89%, 2 steps) of **S12** as a crystalline solid; $[\alpha]_{\text{D}}^{18.7} -136.8$ (*c* 0.40, MeOH); IR (neat) 742, 941, 1171, 1219, 1272, 1384, 1471, 1636, 1732, 2111, 2870, 2926, 2955, 3299 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 7.32-7.18 (m, 5H), 5.23-5.07 (m, 3H), 3.64-3.34 (m, 3H), 2.76-2.70 (m, 1H), 2.67 (s, 3H), 2.51-2.47 (m, 1H), 2.27-1.88 (m, 5H), 1.69-1.16 (m, 7H), 1.12 (d, $J=10.0$ Hz, 3H), 1.02 (d, $J=5.0$ Hz, 3H), 0.99 (d, $J=10.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.9, 170.3, 138.9, 136.3, 135.9, 129.7, 128.7, 126.8, 84.3, 73.0, 68.9, 67.2, 44.5, 43.3, 39.7, 34.7(2 peaks), 34.0, 30.5, 27.1, 24.4, 20.2, 19.6, 18.9, 18.7; HRMS (ESI): Exact mass calcd for $\text{C}_{27}\text{H}_{38}\text{NO}_3$ $[\text{M}+\text{H}]^+$: 424.2852, found: 424.2854.



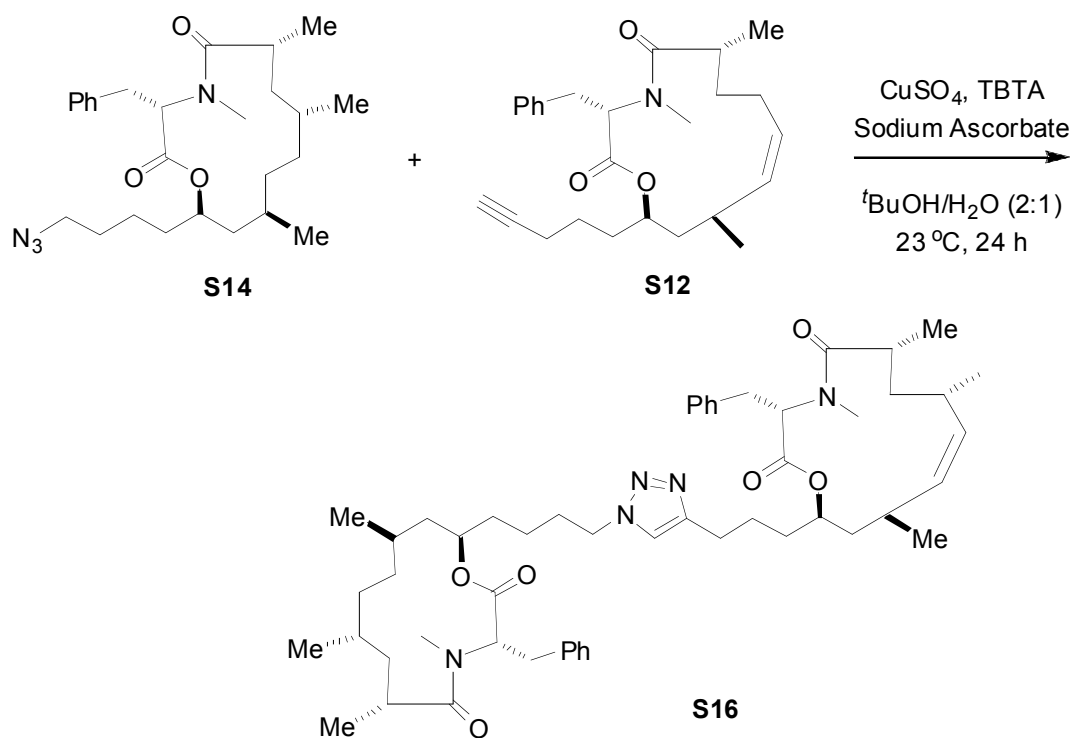
The solution of 16 mg (0.04 mmol) of **S12** and 4.3 mg (0.004 mmol) of 10% Pd/C in 1 mL of MeOH was putted in to a hydrogenation bomb. The hydrogen pressure was raised to 30 bar and the reaction was let go for 24 h. The mixture was filtered on a plug of silica gel (5 cm), washed with MeOH, and concentrated to give 16 mg (93%) of free saturated macrolactone **S13** as a white solid. $[\alpha]^{18.9}_{\text{D}}$ -185 (*c* 0.68, CHCl₃); IR (neat) 702, 752, 1079, 1173.73, 1212, 1276, 1456, 1634, 1738, 2853, 2922, 2956, 3431 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.16 (m, 5H), 5.17-5.10 (m, 1H), 3.58-3.49 (m, 2H), 3.35-3.31 (m, 1H), 2.86-2.76 (m, 1H), 2.66 (s, 3H), 2.01 (t, *J* = 10.0 Hz, 1H), 2.03-1.31 (m, 9H), 1.13 (d, *J* = 5.0 Hz, 3H), 1.08-0.72 (m, 17H); ¹³C NMR (75 MHz, CDCl₃) δ 177.0, 170.3, 139.1, 129.7, 128.6, 126.7, 73.7, 67.2, 39.9, 39.4, 37.1, 36.0, 34.6, 33.6, 32.6, 32.1, 31.7, 27.5, 25.3, 24.3, 22.8, 22.5, 21.6, 19.1, 14.3. HRMS (ESI): Exact mass calcd for C₂₇H₄₄NO₃[M+H]⁺ 430.3321. Found 430.3315.



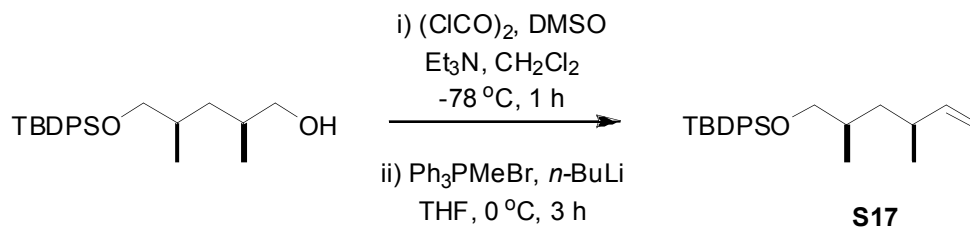
Ph₃P (52 mg, 0.2 mmol) and imidazole (20 mg, 0.3 mmol) were dissolved in CH₂Cl₂ (1 mL) and cooled to 0 °C. I₂ (51 mg, 0.2 mmol) was added in one portion and the reaction was stirred for 10 min at 0 °C. The solution of **S10** (43 mg, 0.1 mmol) in CH₂Cl₂ (1 mL) was added and the reaction mixture was allowed to stir for additional 30 min. The reaction was quenched with NaHCO₃(s) (1 mL) and the layers were separated. Aqueous layer was extracted with CH₂Cl₂ (2 mL x 3). The combined organic layer was dried over MgSO₄, and concentrated. Purification by column chromatography (silica gel, 90/10 hexanes-EtOAc) gave 27 mg (50%) of primary alkyl iodine as a colorless oil. The above product (25 mg, 0.05 mmol) was dissolved in anhydrous DMSO (1 mL) and NaN₃ (33 mg, 0.5 mmol) was added. After 2 h, TLC indicated all the starting material was consumed. The reaction was diluted with Et₂O (2 mL) and washed with H₂O (1 mL x 3) and brine (1 mL). The aqueous layer was also extracted with Et₂O (5 mL x 3). The combined organic layers were dried (Na₂SO₄) and concentrated. Purification by column chromatography (silica gel, 90/10 hexanes-EtOAc) gave 17 mg (50%) of **S14** as a crystalline solid.



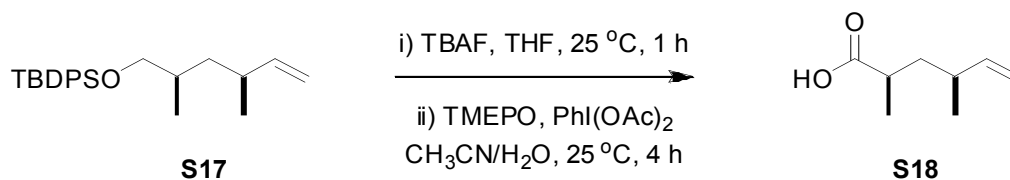
S14 (8.0 mg, 0.017 mmol) and **(-)-spongidepsin** (7.5 mg, 0.017 mmol) were dissolved in ^tBuOH/H₂O (0.6 mL, 2:1). Sodium ascorbate (67 mg, 0.34 mmol), the solution of CuSO₄ (14 mg, 0.085 mmol) in H₂O (0.15 mL) and TBTA (45 mg, 0.085 mmol) were added sequentially. The reaction was stirred for 24 h at 23 °C. Then it was quenched with NaHCO₃(s) (2 mL) and diluted with CH₂Cl₂ (5 mL). The layers were separated, and aqueous layer was extracted with CH₂Cl₂ (5 mL x 3). The combined organic layer was dried over MgSO₄, and concentrated. Purification by column chromatography (silica gel, 60/40 hexanes-EtOAc) gave 12 mg (84%) of desired dimer **S15** as a colorless solid. $[\alpha]_D^{21}$ -157 (c 1.17, CHCl₃); IR (neat) 752, 1079, 1212, 1222, 1275, 1297, 1363, 1460, 1632, 1639, 1731, 1736, 2853, 2869, 2925, 2955 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 7.34-7.16 (m, 10H), 5.18-5.10 (m, 2H), 4.34-4.31 (m, 2H), 3.70-3.46 (m, 5H), 3.30-3.25 (m, 2H), 2.83-2.71 (m, 2H), 2.66 (s, 3H), 2.65 (s, 3H), 2.10-0.73 (m, 50H); ¹³C NMR (75 MHz, CDCl₃) 177.1 (2 peaks), 170.5, 170.4, 148.0, 138.9 (2 peaks), 129.7, 128.7, 128.6, 126.7 (2 peaks), 121.0, 73.3, 72.9, 67.0, 50.1, 39.9, 39.8, 39.3, 37.3, 37.2, 35.6, 35.3, 34.6, 33.5, 32.5, 31.6 (2 peaks), 30.3, 27.5, 25.8, 25.7, 24.3 (2 peaks), 22.6, 22.5, 21.6, 19.0. HRMS (ESI): Exact mass calcd for C₅₃H₈₀N₅O₆[M+H]⁺ 882.6109. Found 882.6107.



S14 (8.0 mg, 0.017 mmol) and **S12** (7.5 mg, 0.017 mmol) were dissolved in $t\text{BuOH/H}_2\text{O}$ (0.6 mL, 2:1). Sodium ascorbate (67 mg, 0.34 mmol), the solution of CuSO_4 (14 mg, 0.085 mmol) in H_2O (0.15 mL) and TBTA (45 mg, 0.085 mmol) were added sequentially. The reaction was stirred for 24 h at 23 $^\circ\text{C}$. Then it was quenched with $\text{NaHCO}_3(\text{s})$ (2 mL) and diluted with CH_2Cl_2 (5 mL). The layers were separated, and aqueous layer was extracted with CH_2Cl_2 (5 mL x 3). The combined organic layer was dried over MgSO_4 , and concentrated. Purification by column chromatography (silica gel, 60/40 hexanes-EtOAc) gave 12 mg (87%) of desired dimer **S16** as a colorless solid. $[\alpha]_D^{21}$ -156 (c 0.99, CHCl_3); IR (neat) 701, 753, 1011, 1079, 1173, 1218, 1275, 1297, 1377, 1412, 1460, 1631, 1640, 1731, 1736, 2853, 2928, 2955, 3031 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) 7.32-7.16 (m, 10H), 5.21-5.05 (m, 4H), 4.34-4.31 (m, 2H), 3.65-3.31 (m, 6H), 2.76-2.72 (m, 4H), 2.66 (s, 3H), 2.65 (s, 3H), 2.50-2.44 (m, 1H), 2.13-0.72 (m, 44H); ^{13}C NMR (75 MHz, CDCl_3) 177.1, 176.9, 170.5, 170.4, 147.9, 138.9, 136.3, 135.9, 129.7 (2 peaks), 128.7 (2 peaks), 126.7, 121.0, 73.2, 72.9, 67.0 (2 peaks), 50.1, 39.8, 39.7, 35.3, 34.7, 34.6, 33.9, 33.5, 30.4, 30.3, 27.5, 27.1, 24.3, 22.6, 22.5, 21.6, 20.2, 19.6, 19.0, 18.9. HRMS (ESI): Exact mass calcd for $\text{C}_{53}\text{H}_{78}\text{N}_5\text{O}_6[\text{M}+\text{H}]^+$ 880.5952. Found 880.5959.



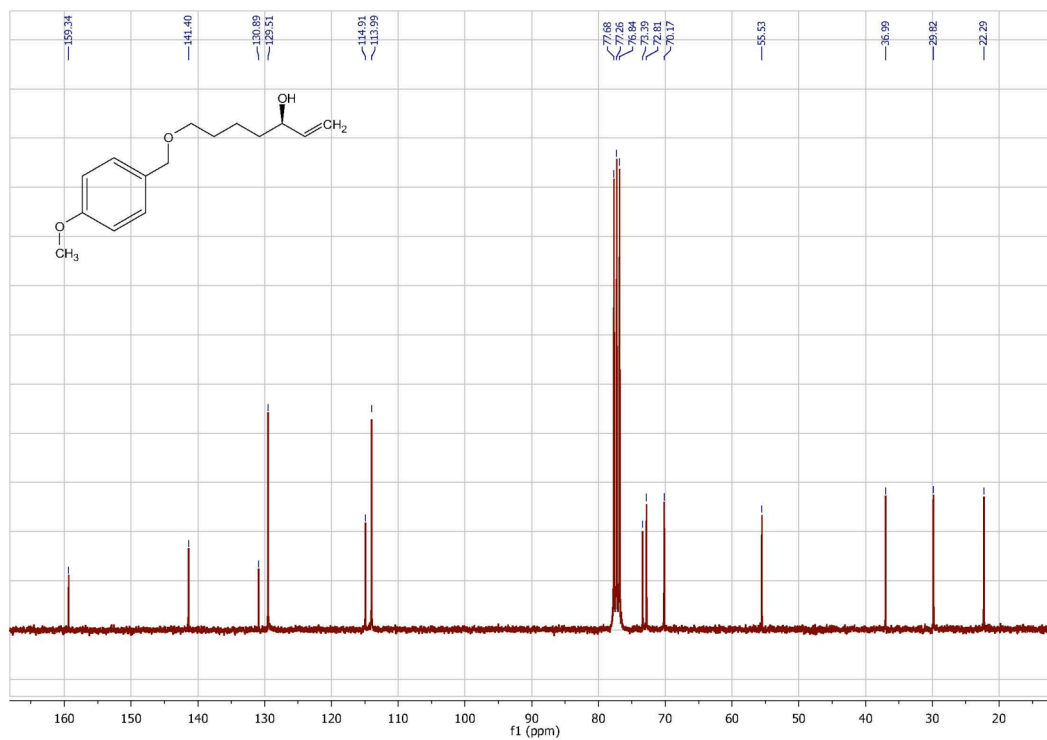
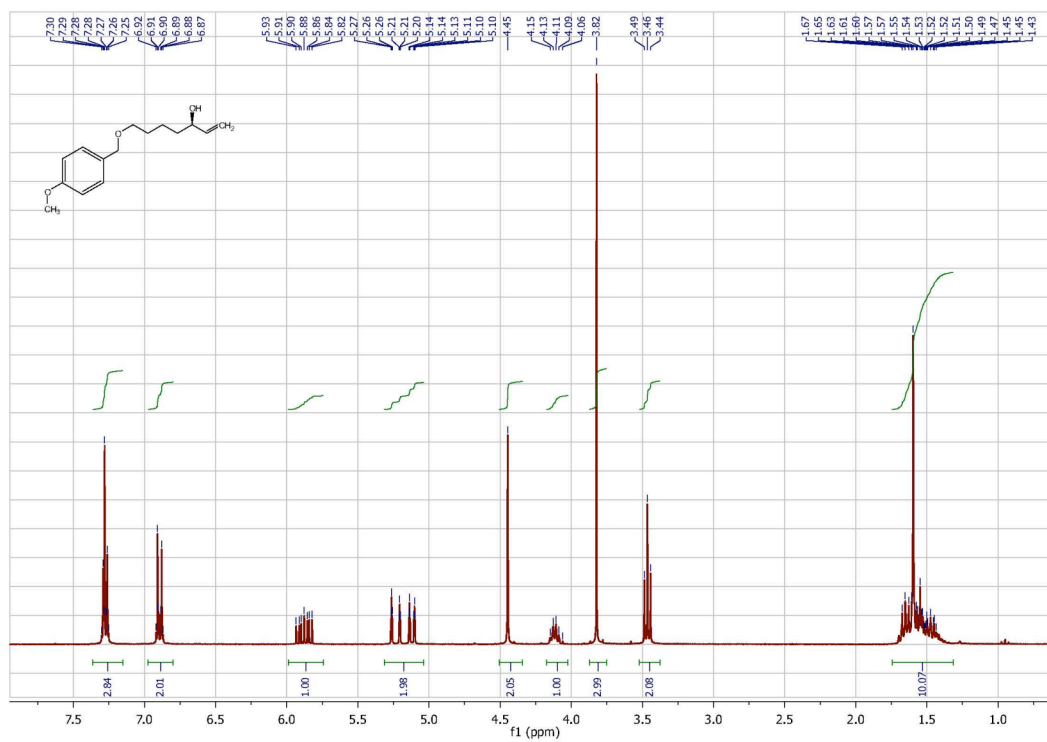
To a solution of oxalyl chloride (0.83 mL, 9.52 mmol) in CH₂Cl₂ (15 mL) at -78 °C was added DMSO (1.27 mL, 21.8 mmol) dropwise. After 5 min, a -78 °C solution of TBDPS protected alcohol (1.68 g, 4.53 mmol)⁵ in CH₂Cl₂ (10 mL, 2 × 1 mL for rinsing) was rapidly added via cannula. After 5 min, Et₃N (3.2 mL, 22.7 mmol) was introduced and the reaction mixture was allowed to warm to 0 °C before NH₄Cl (10 mL) was added followed by Et₂O (25 mL). The layers were separated, the organic layer was washed sequentially with H₂O (2 mL) and brine (3 mL). The organic extract was dried (Na₂SO₄) and concentrated *in vacuo*. The resulting residue was carried out to the next step without any further purification. In a separate round bottom flask, methyltriphenylphosphonium bromide (2.43 g, 6.8 mmol) suspension in THF (15 mL) was cooled to 0 °C and ^{*n*}BuLi (2.5 M in Hexanes, 2.6 mL, 6.6 mmol) was added dropwise. The reaction was stirred for 1 h before the crude aldehyde in THF solution (1.5 mL, 2 × 0.5 mL for rinsing) was cannulated. After 1 h, saturated NH₄Cl aqueous solution (20 mL) was added and the mixture was stirred and allowed to warm to 25 °C. The layers were then separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (5:95) gave alkene **S17**⁶ (1.44 g, 87% over two steps) as a colorless oil.

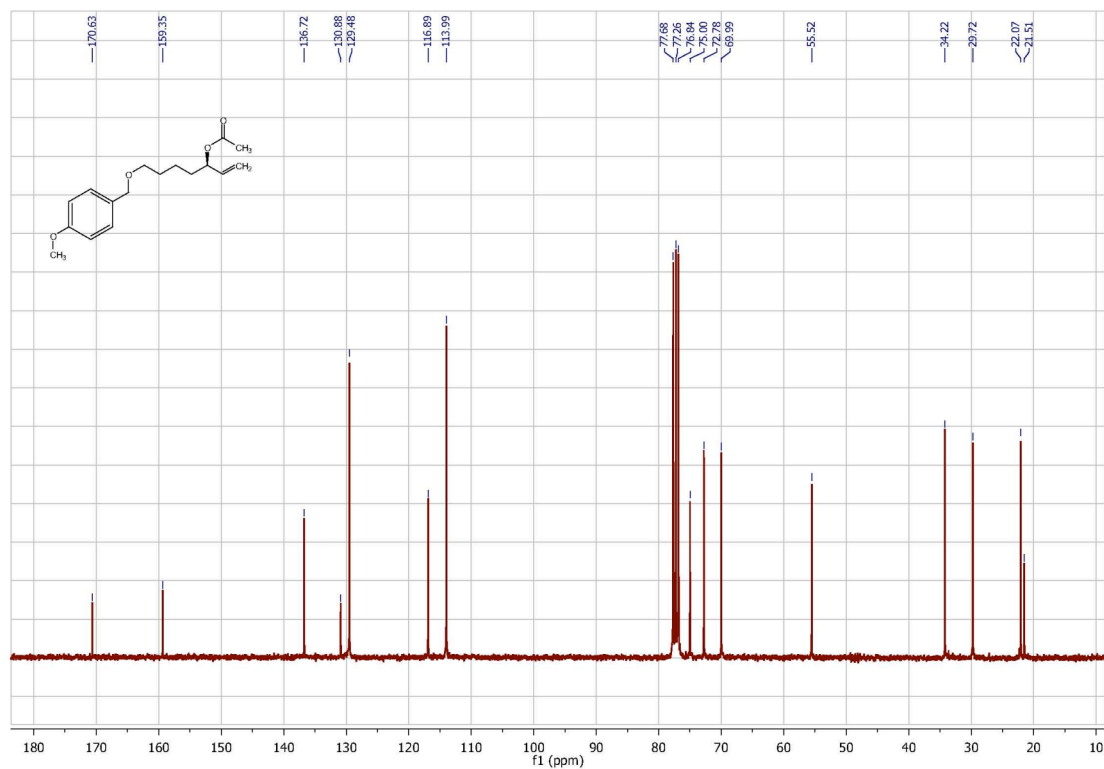
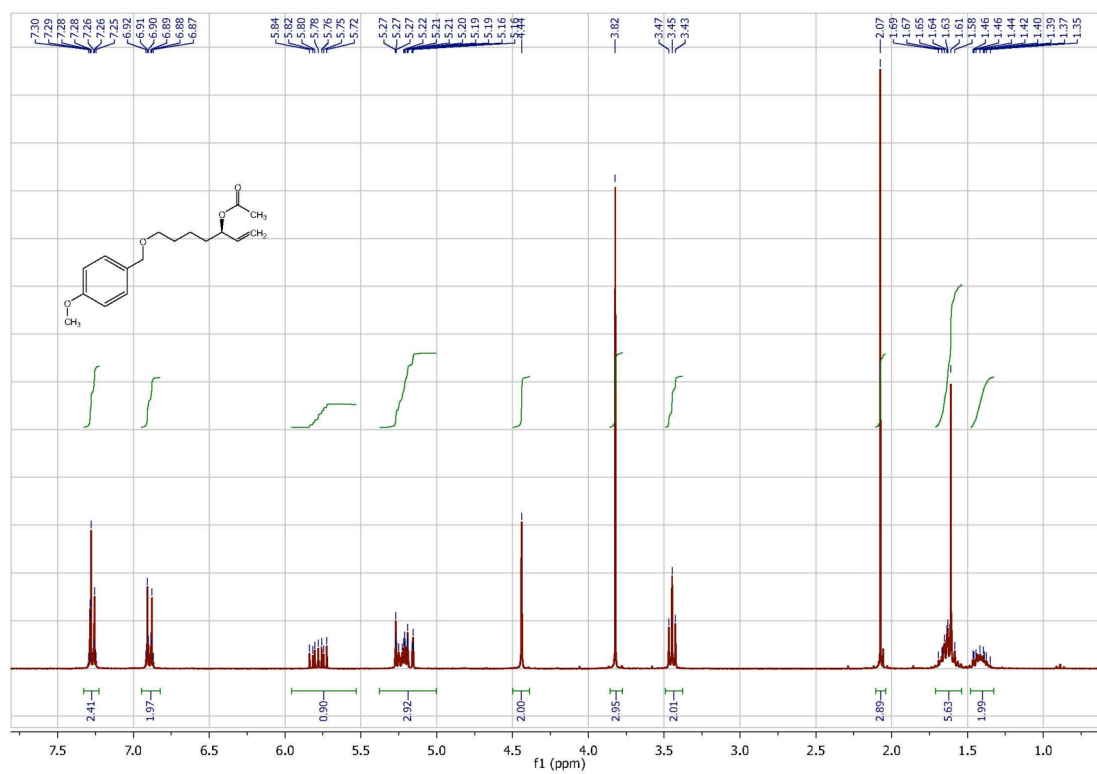


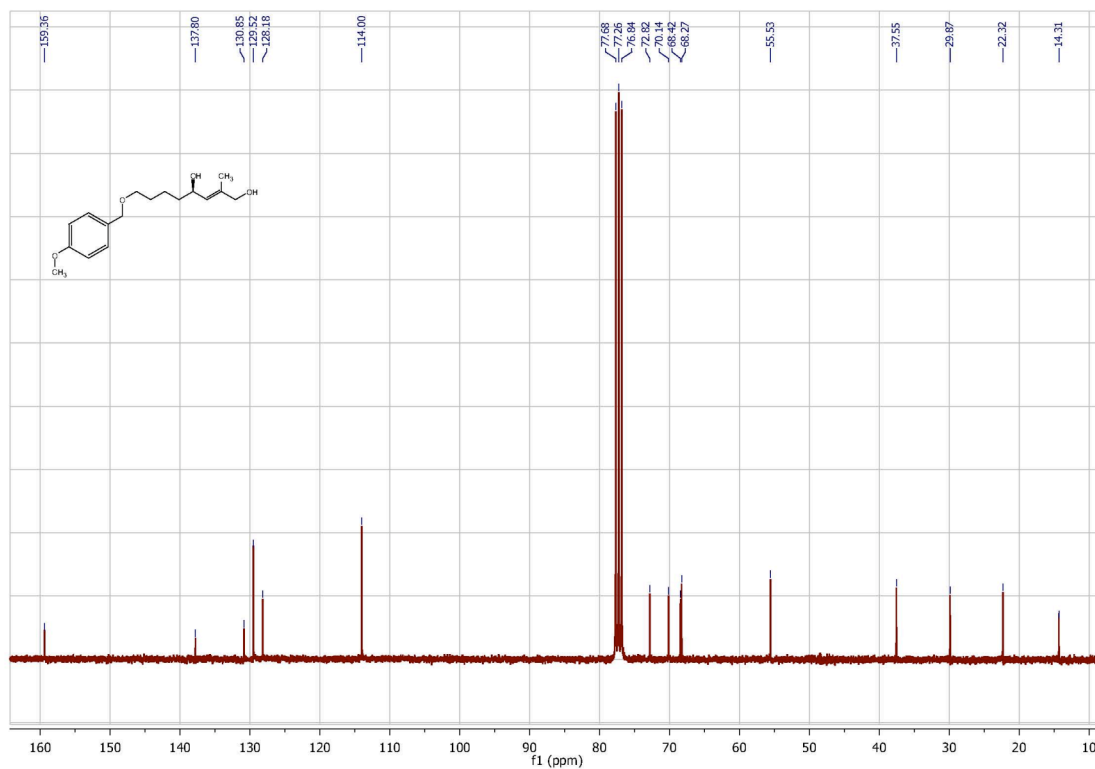
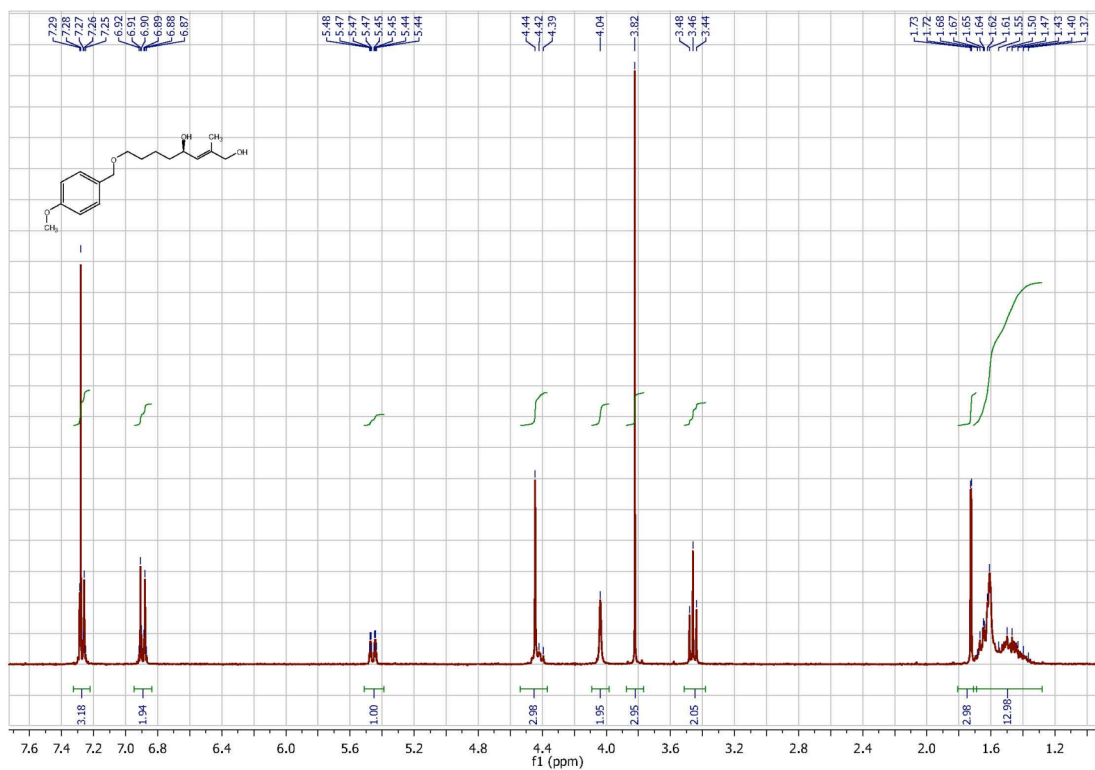
To a solution of compound **S17** (1.44 g, 3.94 mmol) in THF (20 mL) was added dropwise a solution of TBAF (1 M in THF, 4.0 mL, 4.0 mmol) at 25 °C. The reaction was stirred for 1 h, then was diluted with Et₂O (20 mL) and NH₄Cl(s) (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* at 10 °C. Purification by flash column chromatography, eluting with Et₂O/Pentane (15:85) gave alcohol⁷ (0.46 g, 92%) as a colorless oil. The above alcohol (0.21g, 1.6 mmol) was dissolved in CH₃CN/H₂O (1:1, 20 mL). TEMPO (0.50g, 3.2 mmol) and BAIB (1.55g, 4.8mmol) were added in one portion. The mixture was stirred at 25 °C for 4 h, then it was quenched with NH₄Cl(s) (10 mL). The layers were separated and aqueous layer was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (silica gel, 80/20 Hexanes-EtOAc) gave 0.20 g (88%) of unsaturated dimethyl acid **S18**⁵ as colorless oil. $[\alpha]_D^{21}$ -5.8 (*c* 1.03, CHCl₃); IR (neat) 913.33, 996.28, 1242.21, 1418.71, 1464.03, 1706.11, 2930.96, 2975.33, 3081.42 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) 5.71-5.59 (m, 1H), 5.05-4.94 (m, 2H), 2.58-2.46 (m, 1H), 2.30-2.16 (m, 1H), 1.77-1.72 (m, 1H), 1.42-1.33 (m, 1H), 1.19 (d, *J* = 6.0 Hz, 3 H), 1.04 (d, *J* = 6.0 Hz, 3 H); ¹³C NMR (75 MHz, CDCl₃) 183.1, 143.6, 113.8, 40.2, 37.4, 36.1, 20.9, 16.9.

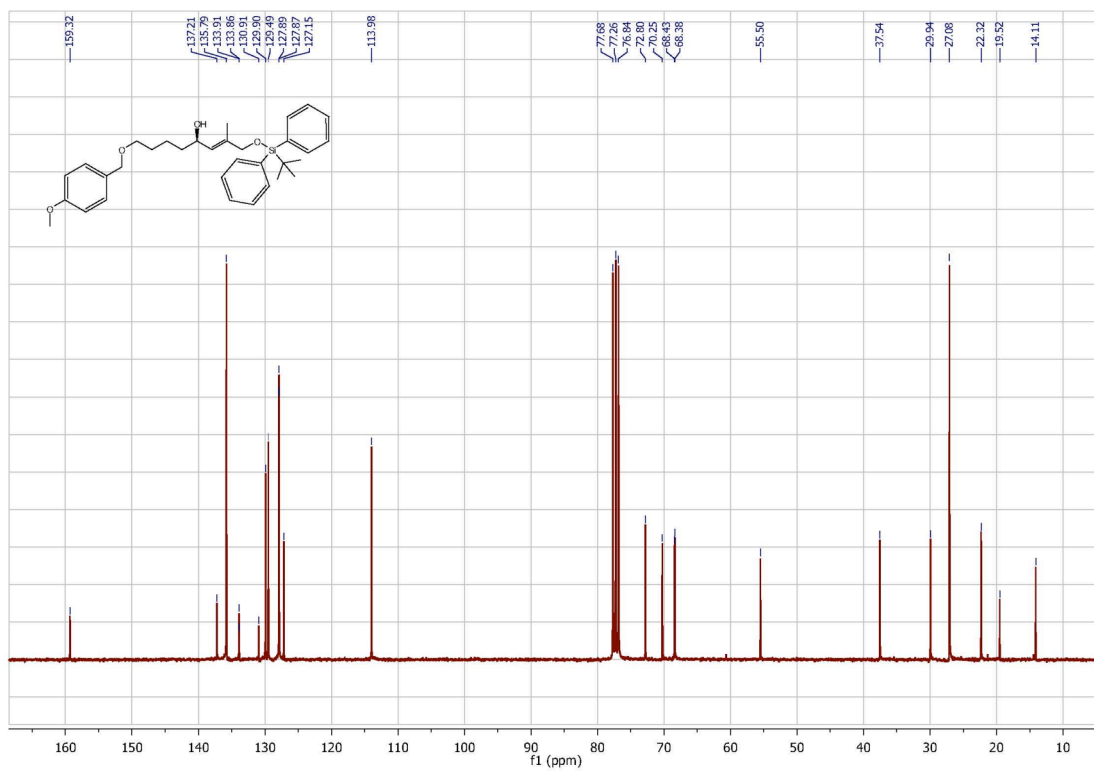
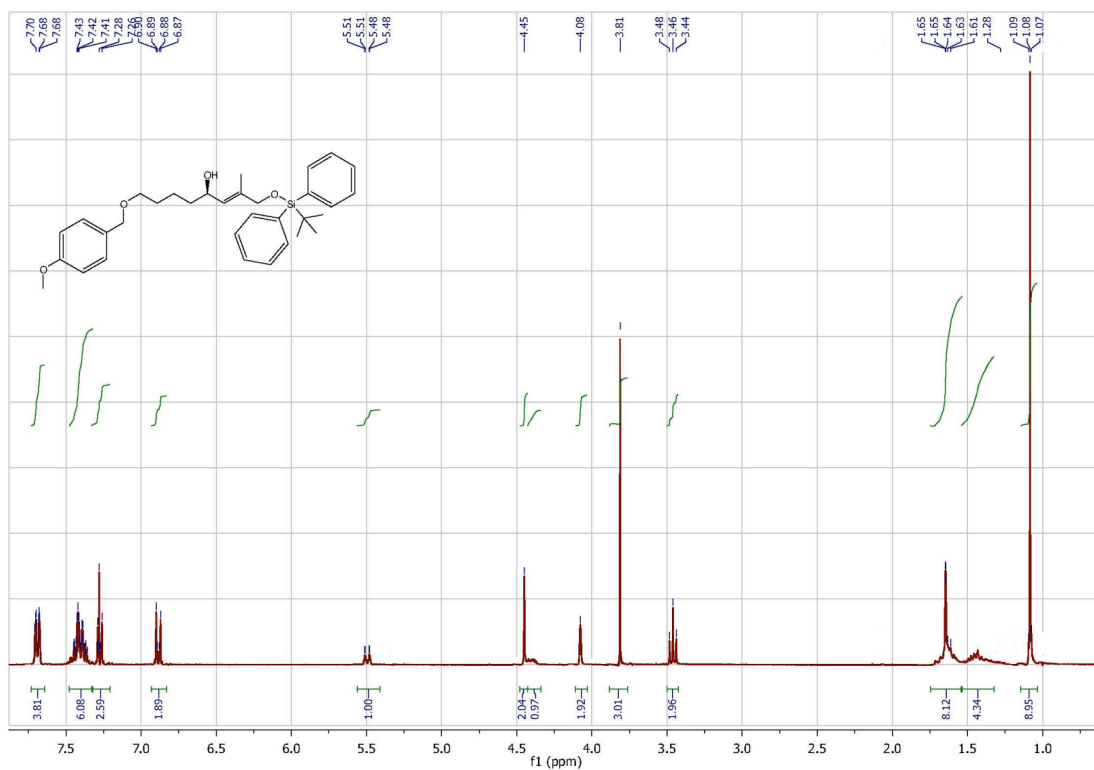
Table C-1. Comparison of ^{13}C NMR of natural and synthetic (-)-spongidepsin

atom number	natural (-)-spongidepsin (δc) ^{5a}	synthetic (-)-spongidepsin (δc)
C1	18.9	19.1
C2	19.1	19.1
C3	21.8	21.8
C4	22.6	22.6
C5	25.4	25.4
C6	25.7	25.7
C7	28.5	28.5
C8	32.7	32.7
C9	33.6	33.6
C10	34.7	34.7
C11	35.4	35.5
C12	35.9	36.0
C13	38.2	38.2
C14	40.5	40.5
C15	40.6	40.6
C16	67.7	67.8
C17	70.1	70.1
C18	74.1	74.2
C19	84.8	84.8
C20	127.8	127.9
C21	129.7	129.7
C22	130.7	130.8
C23	139.7	139.7
C24	172.1	172.1
C25	179.6	179.6

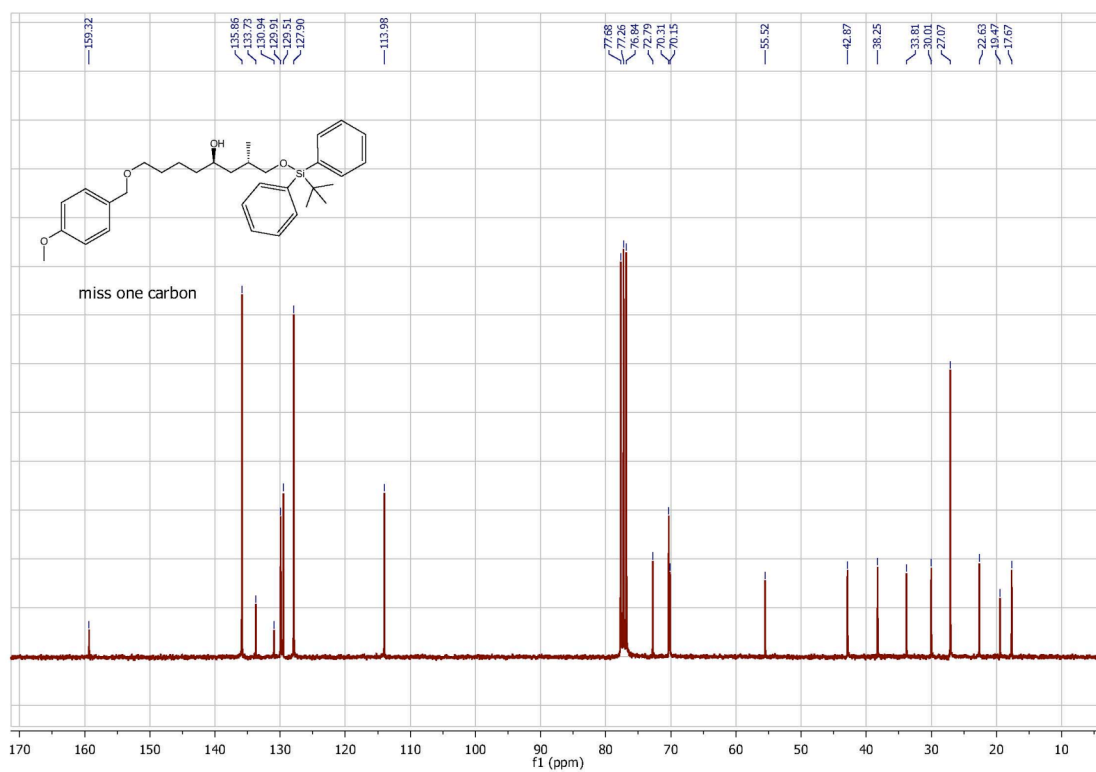
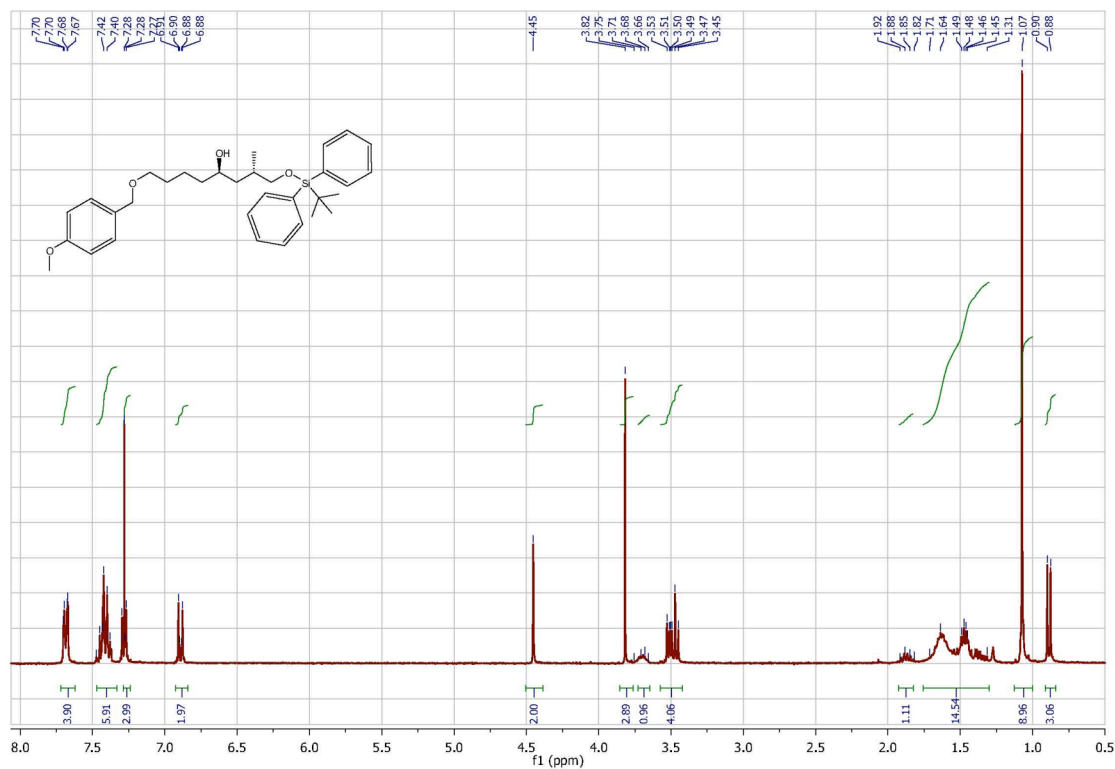
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of (*R*)-**S1**

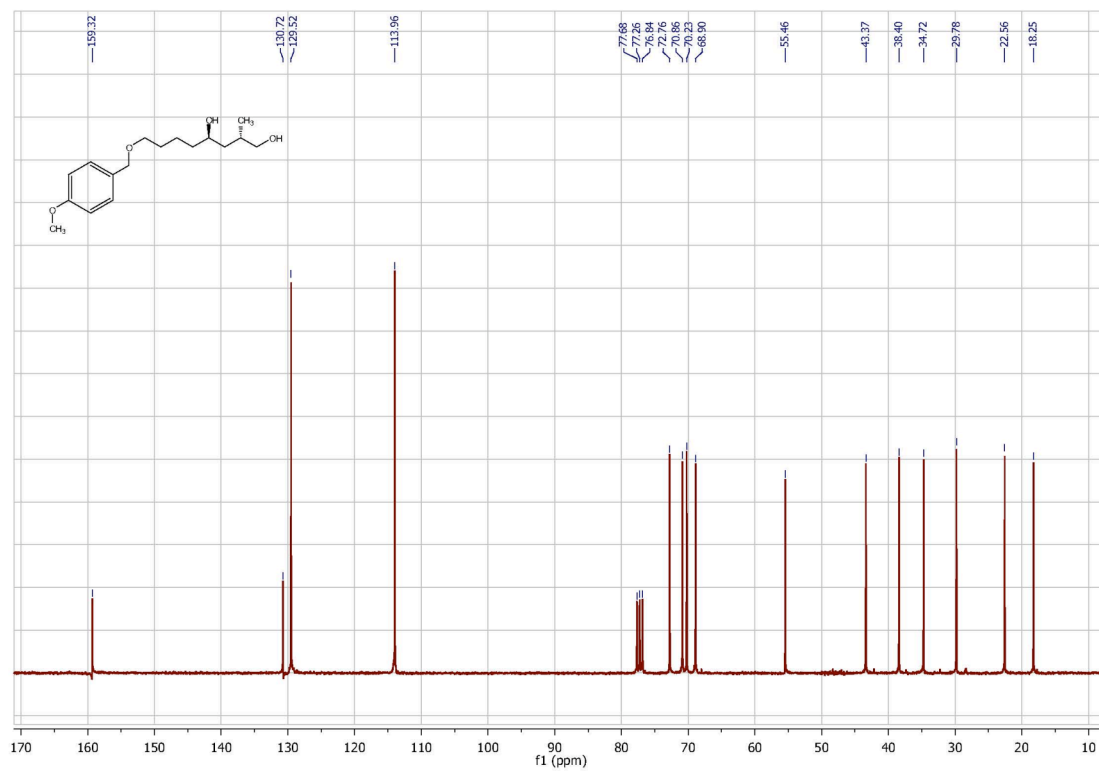
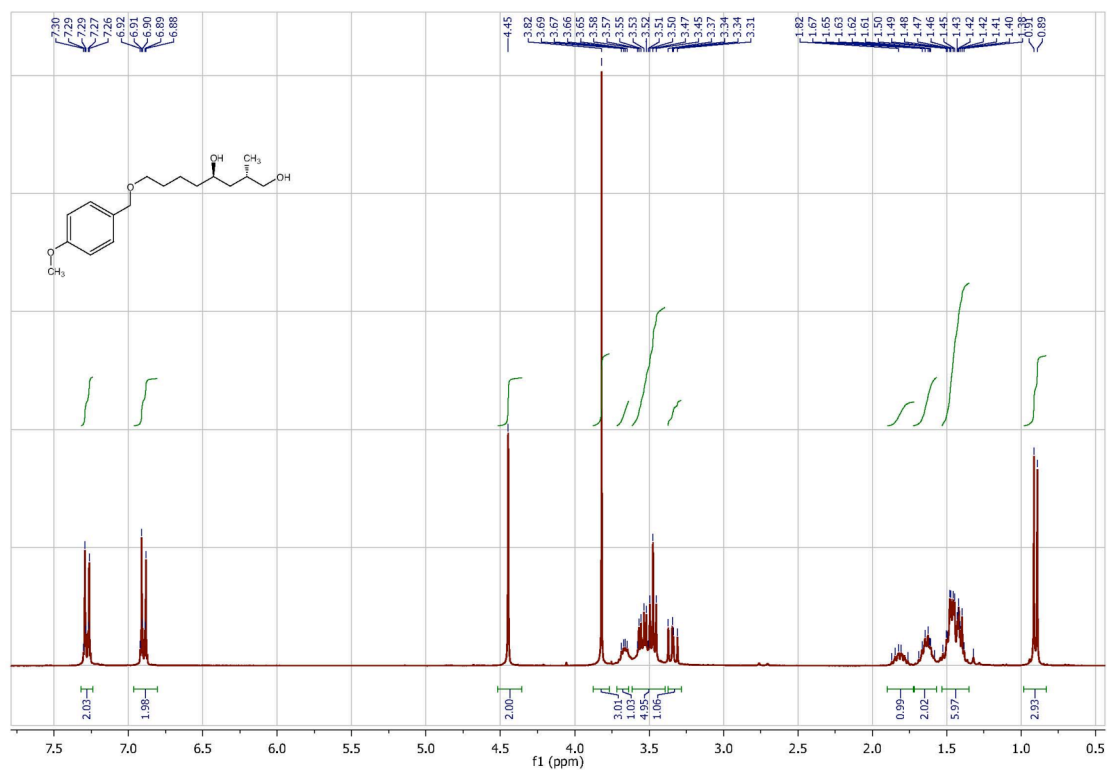
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S2**

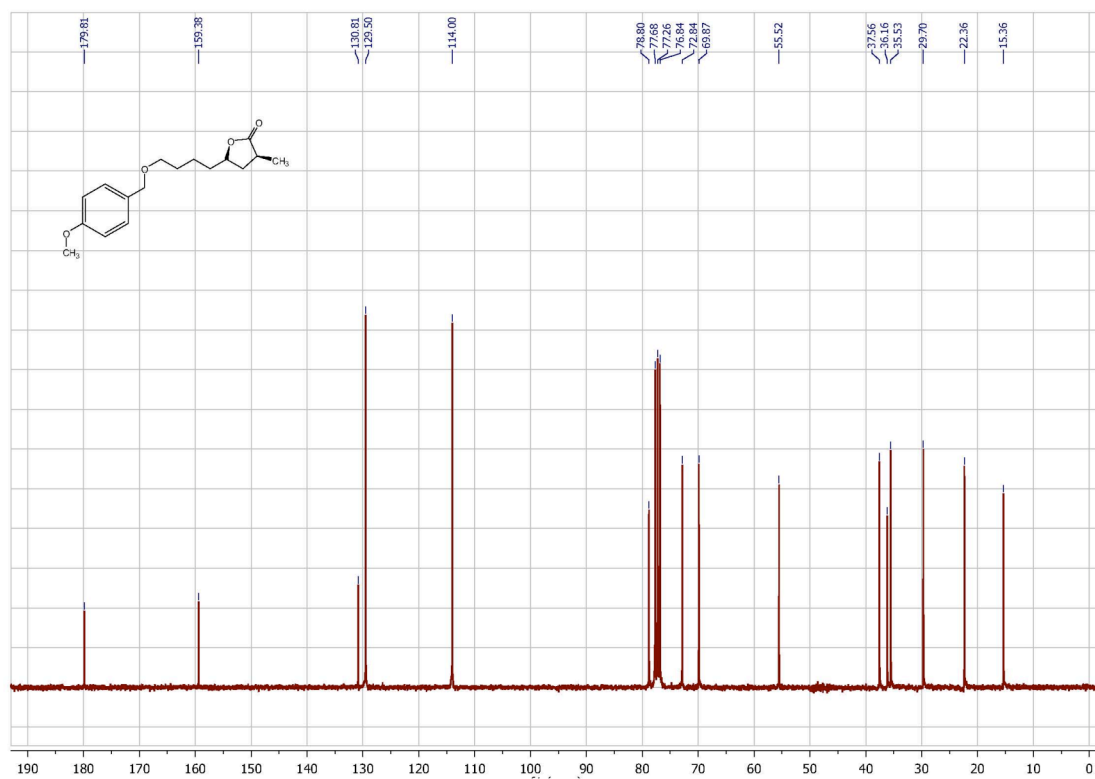
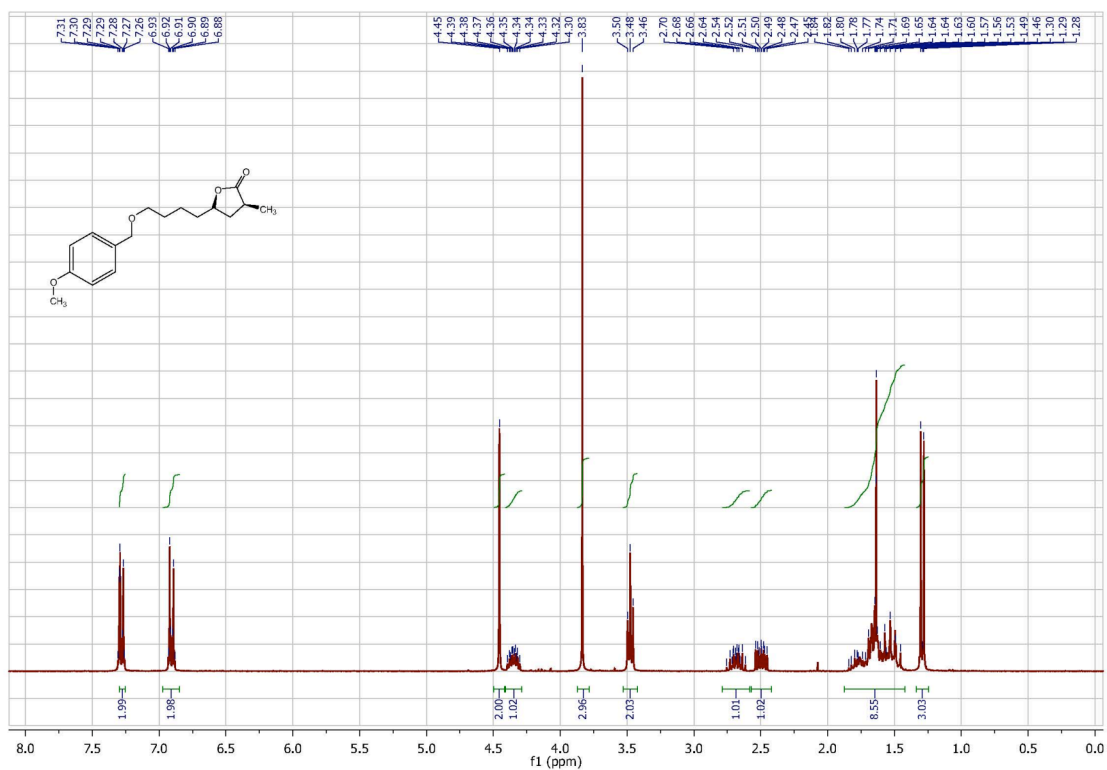
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S3**

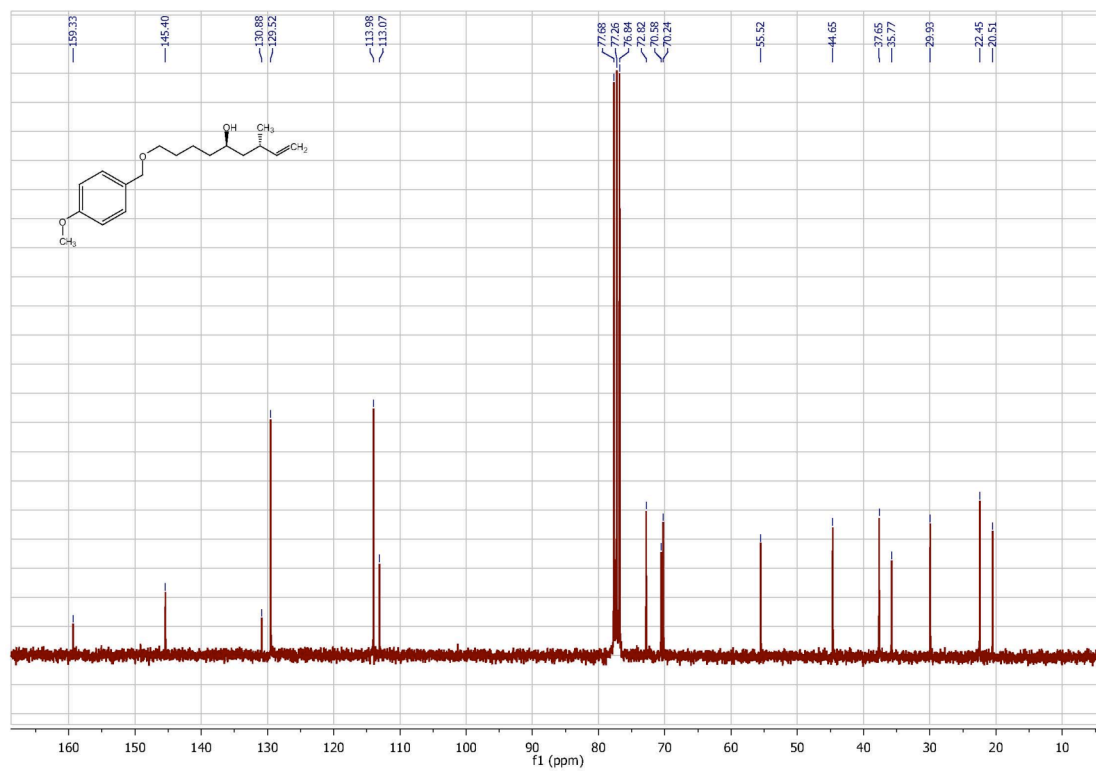
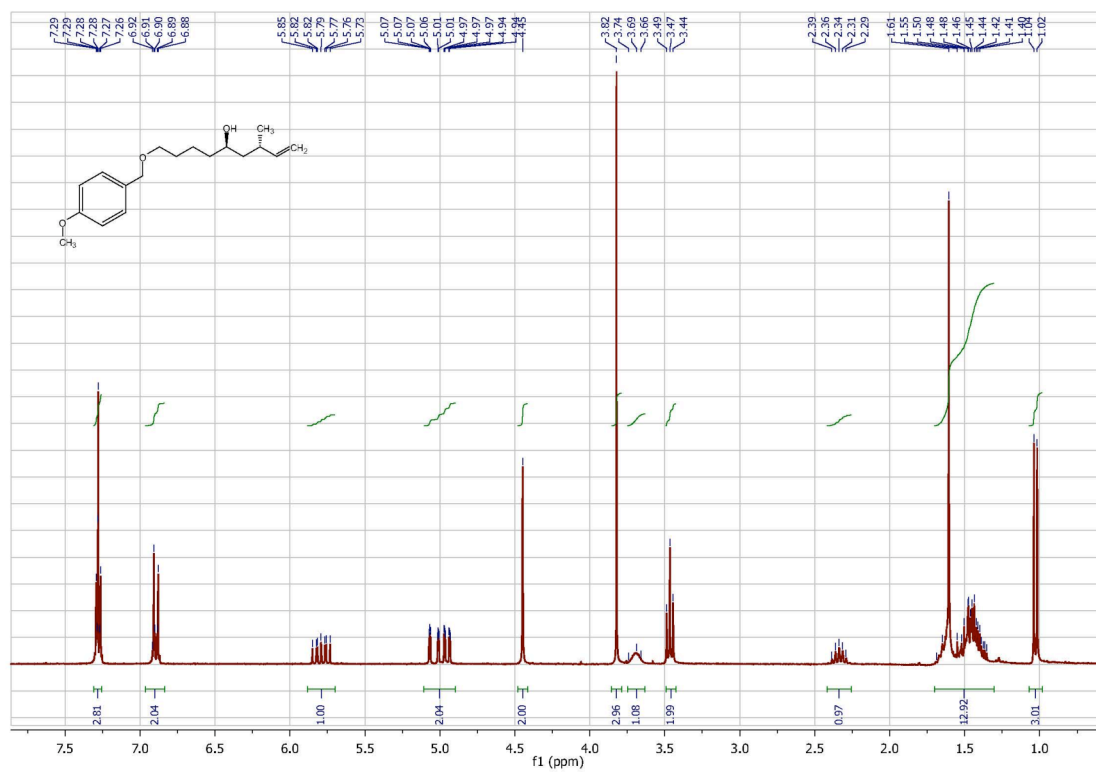
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S4**

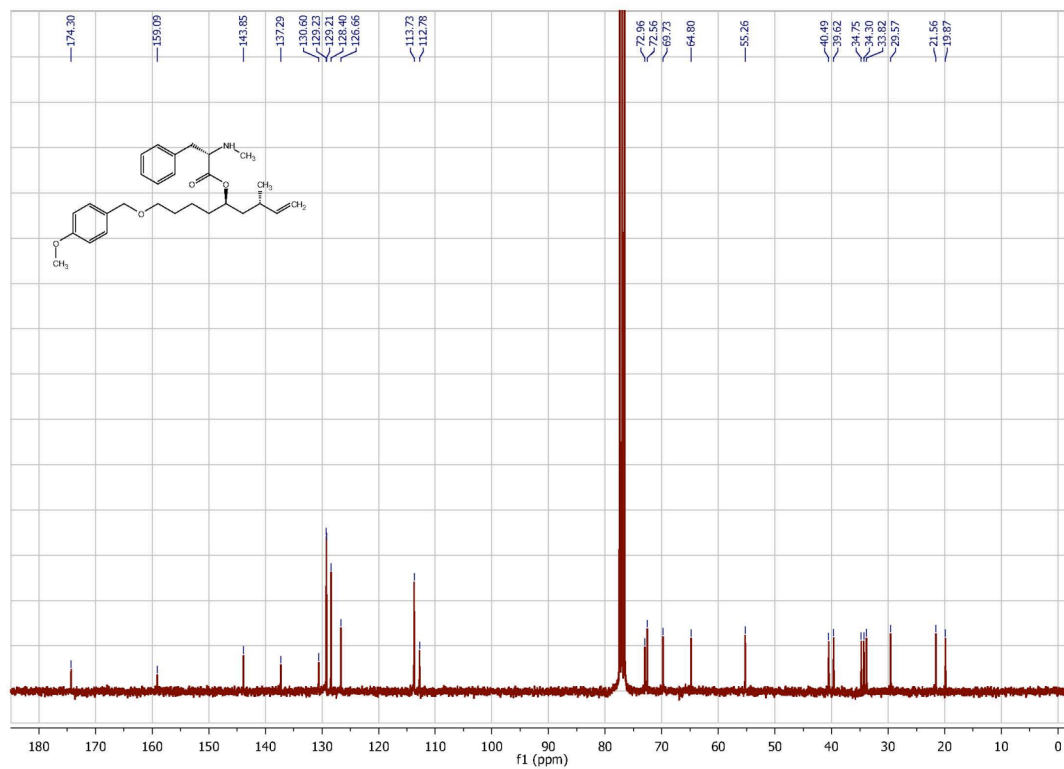
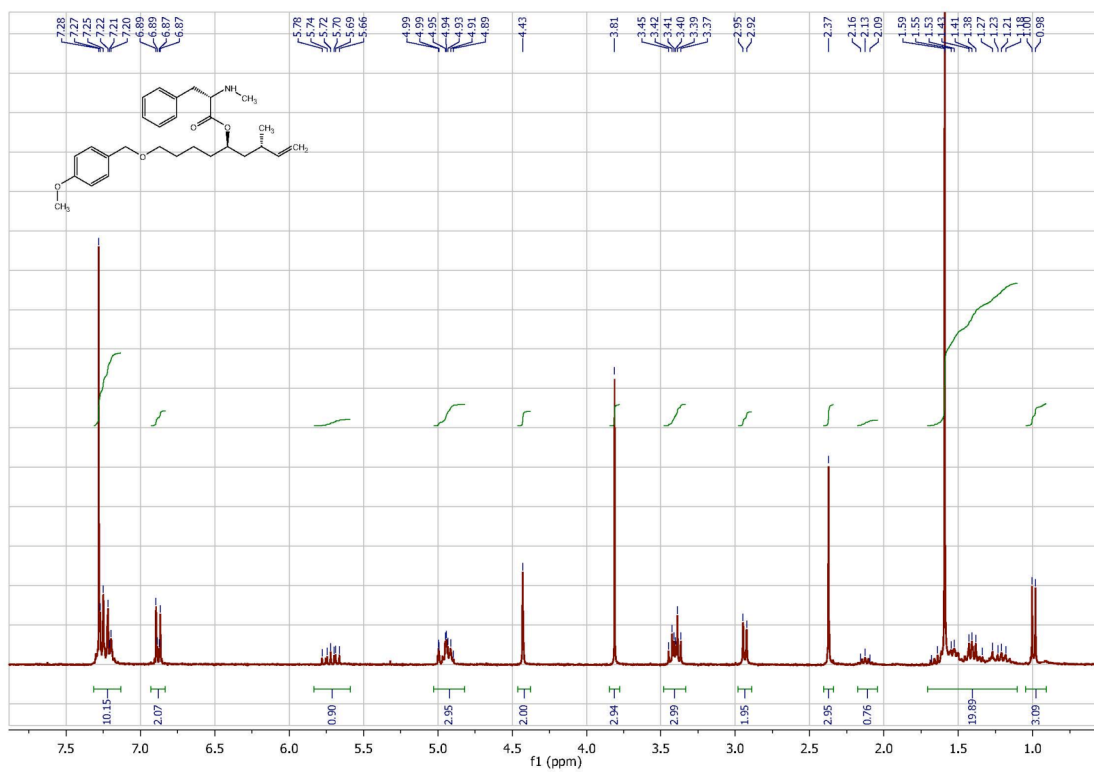
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of hydrogenation product of S4

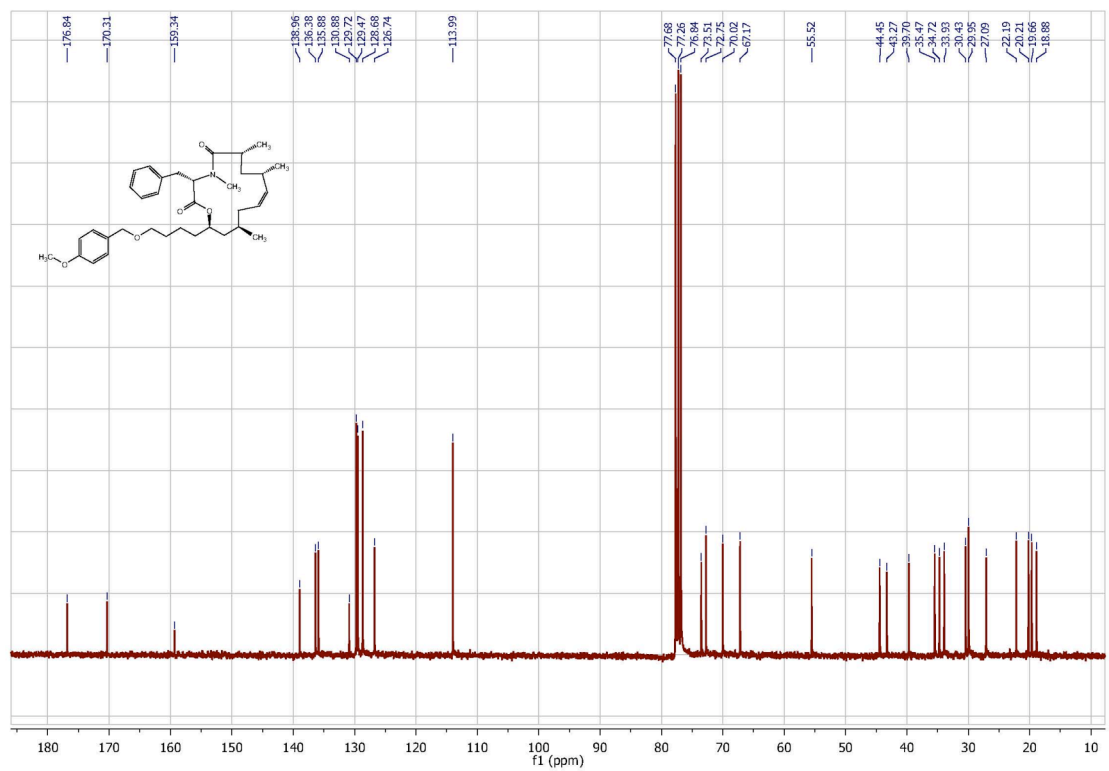
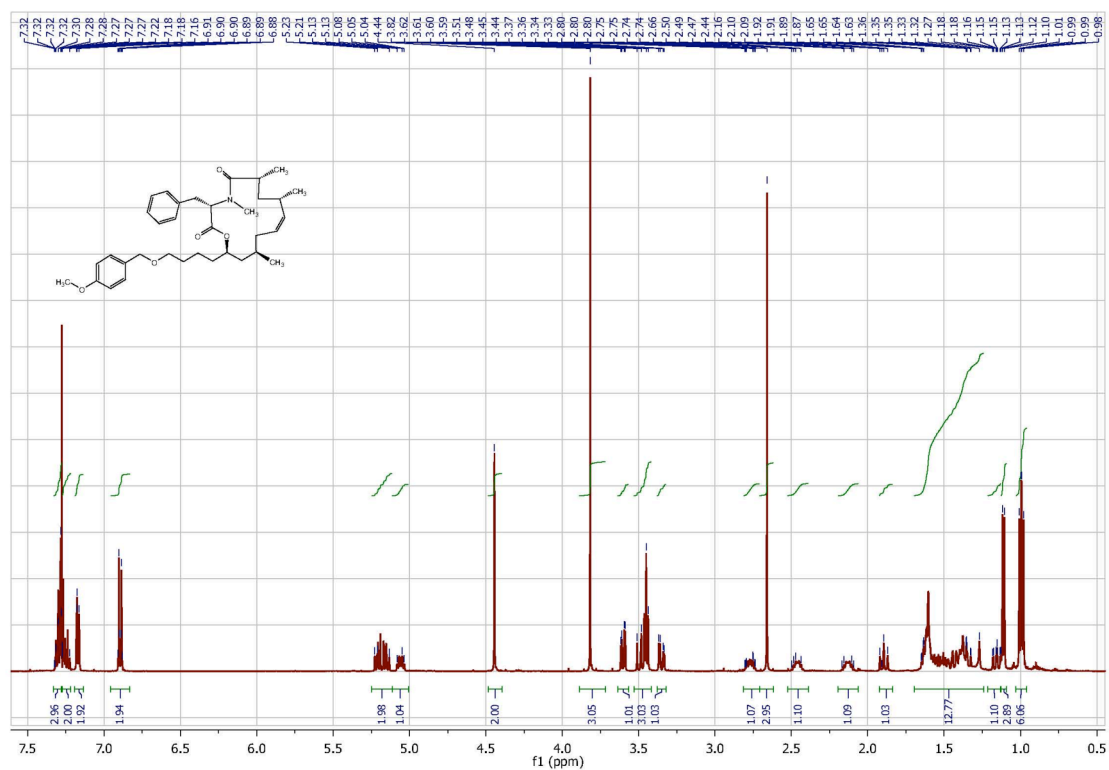


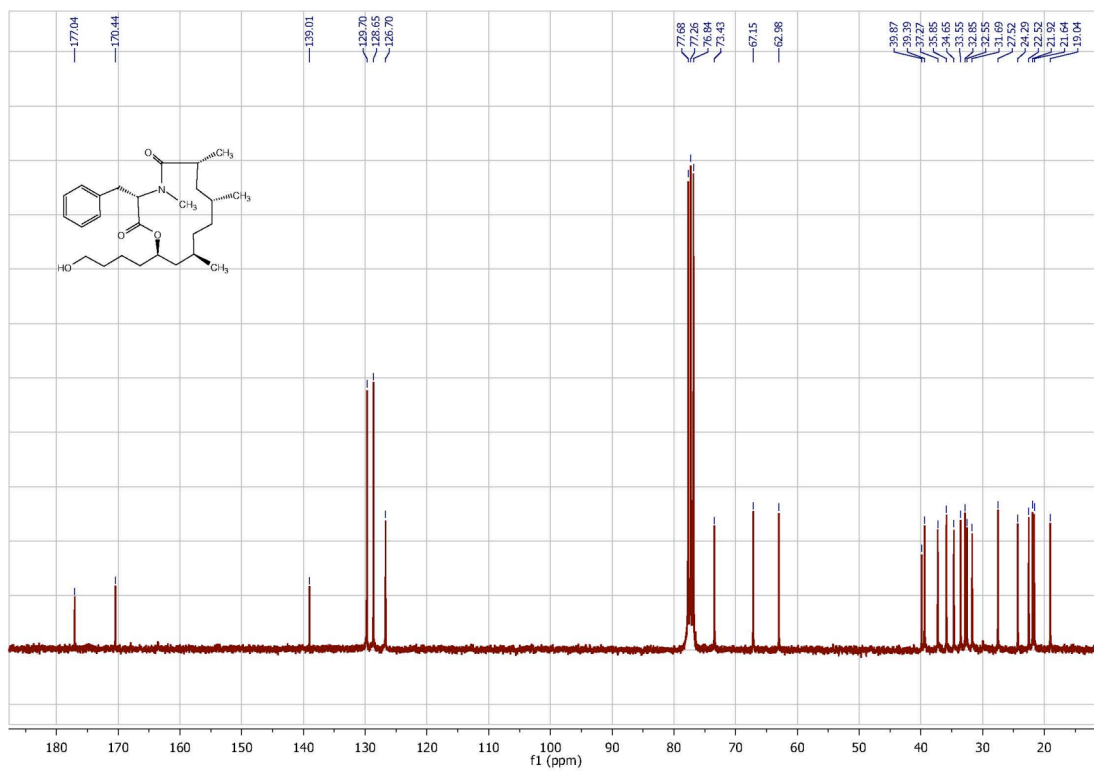
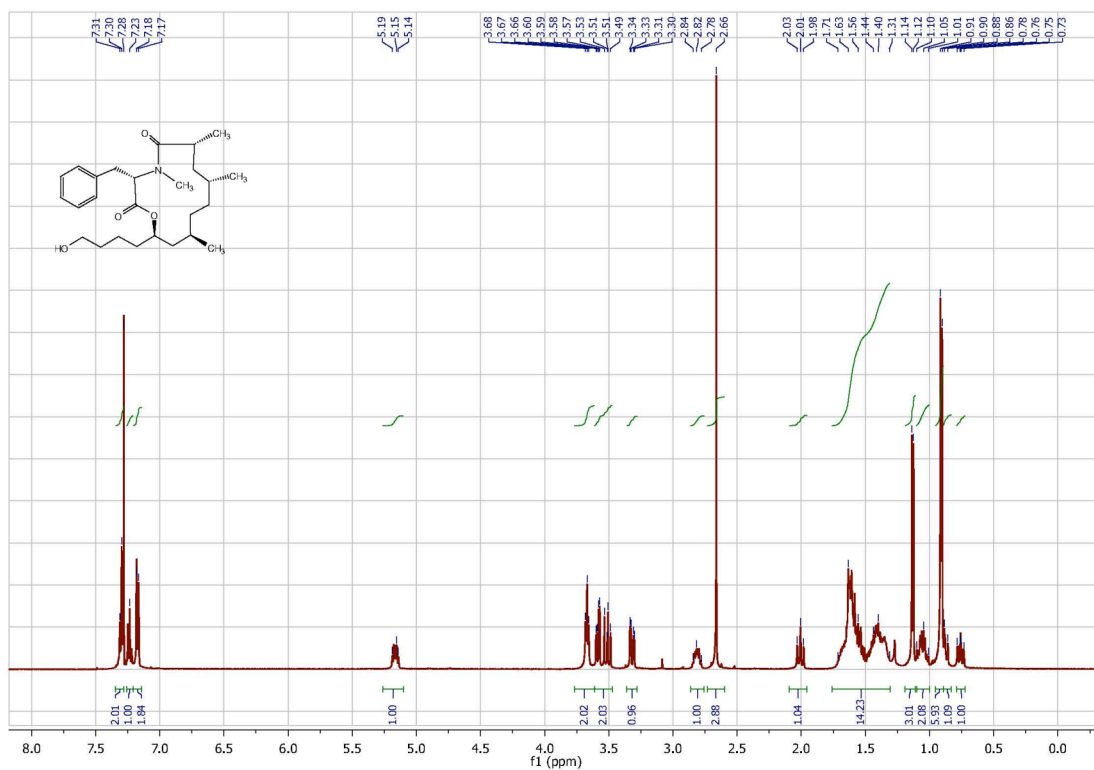
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S5**

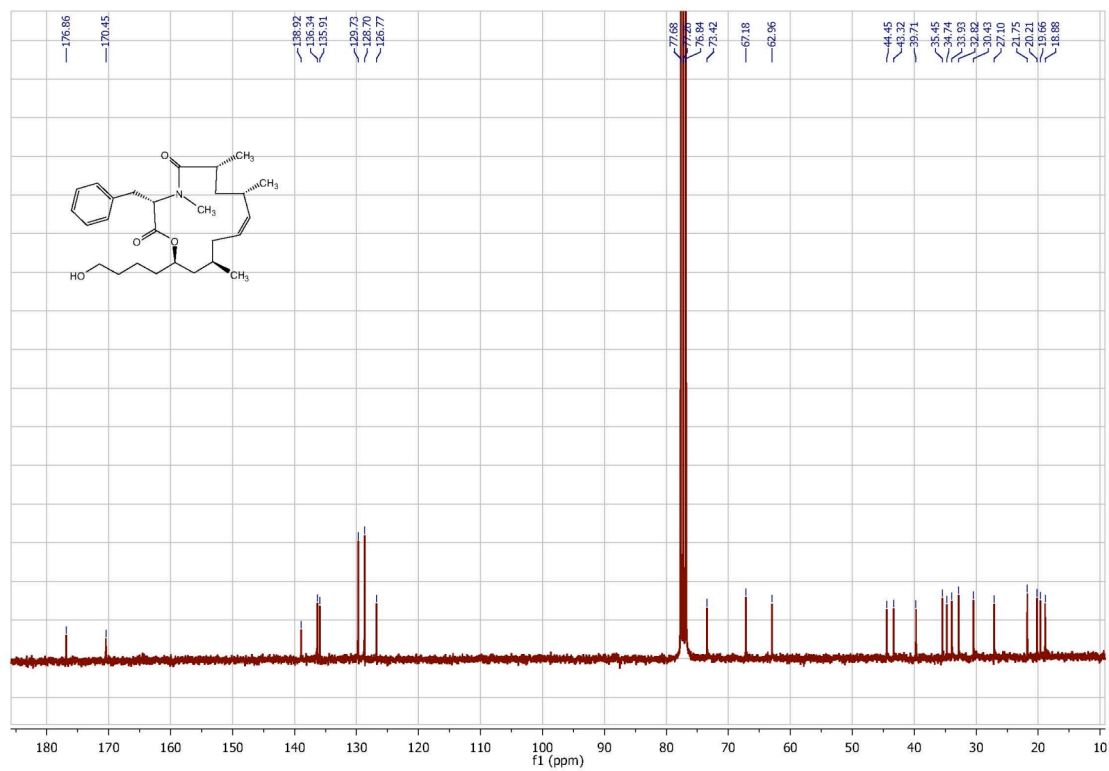
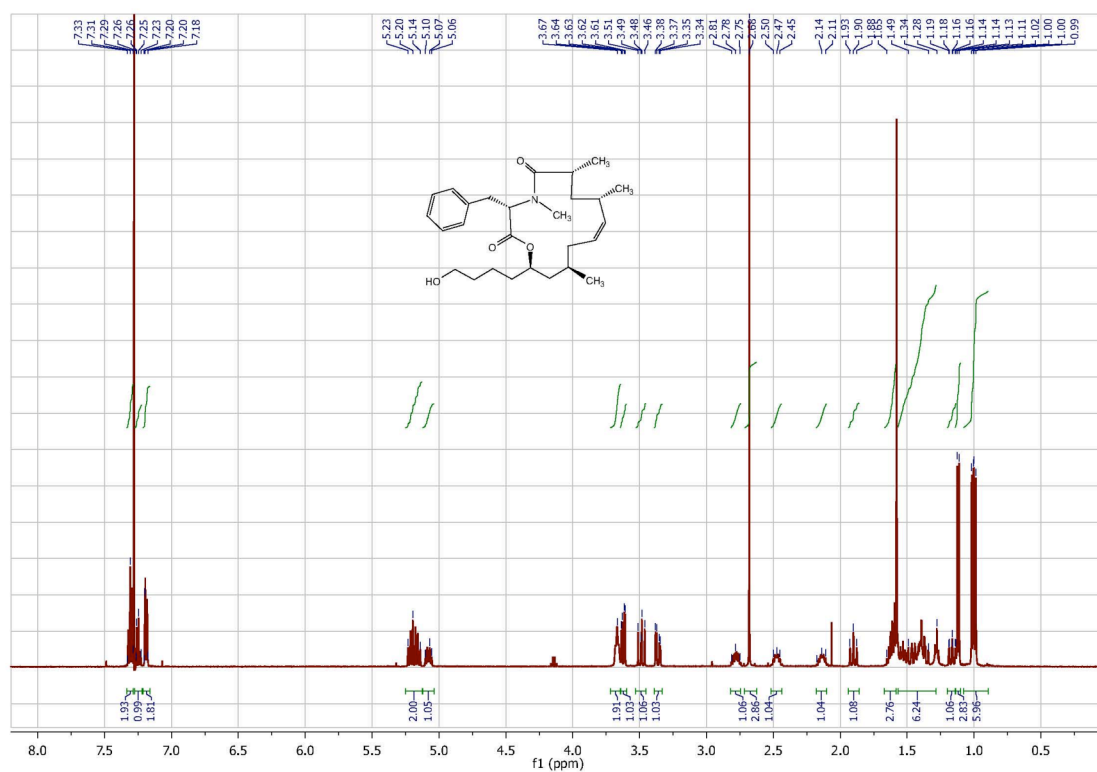
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of S6

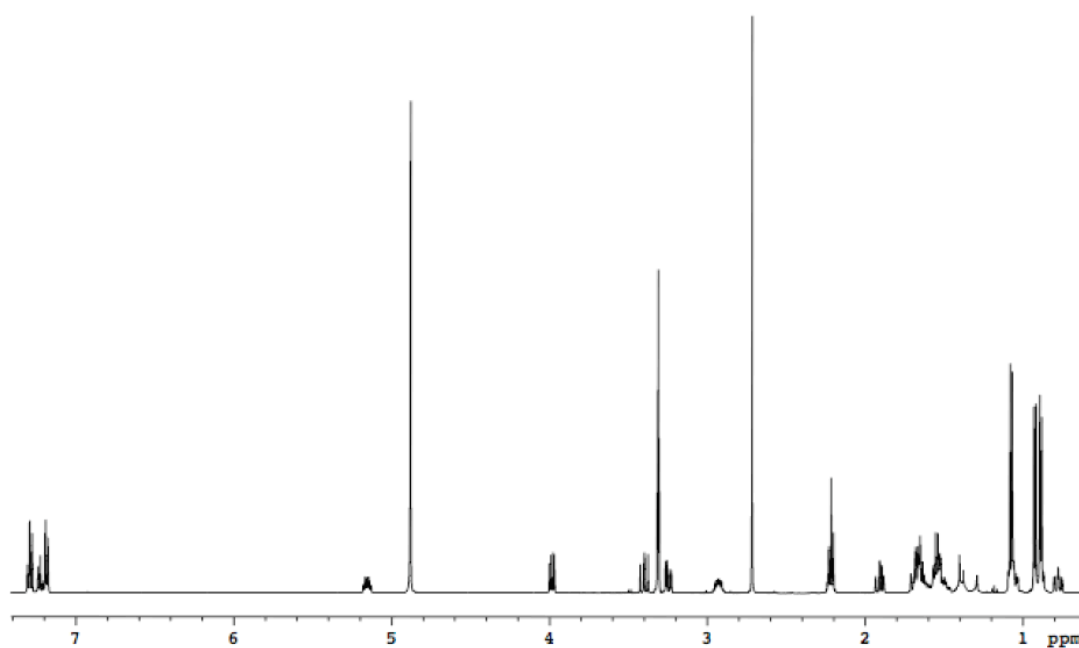
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of S7

^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S8**

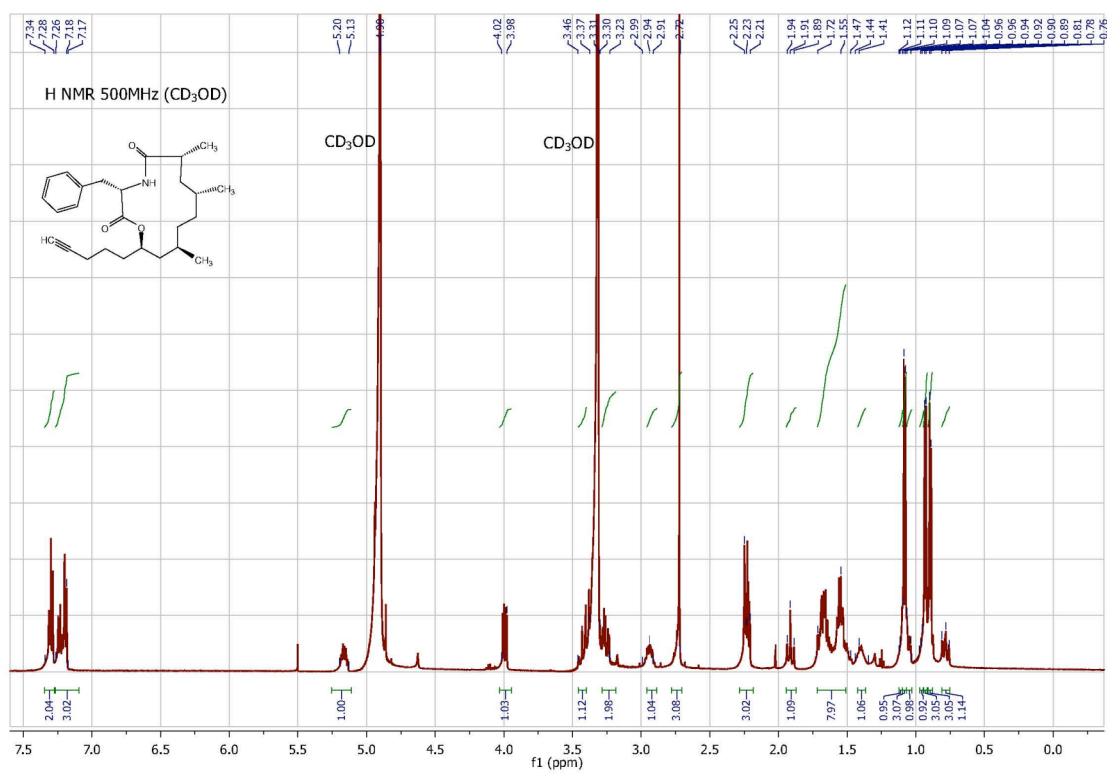
¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) of **S9**

^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S10**

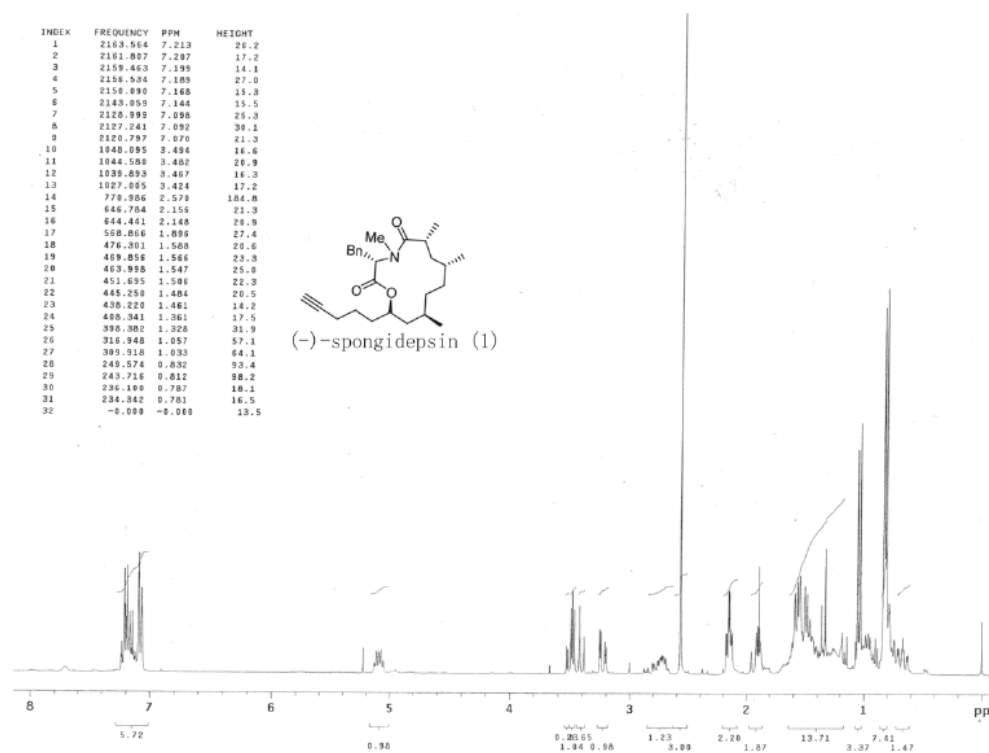
^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S11**



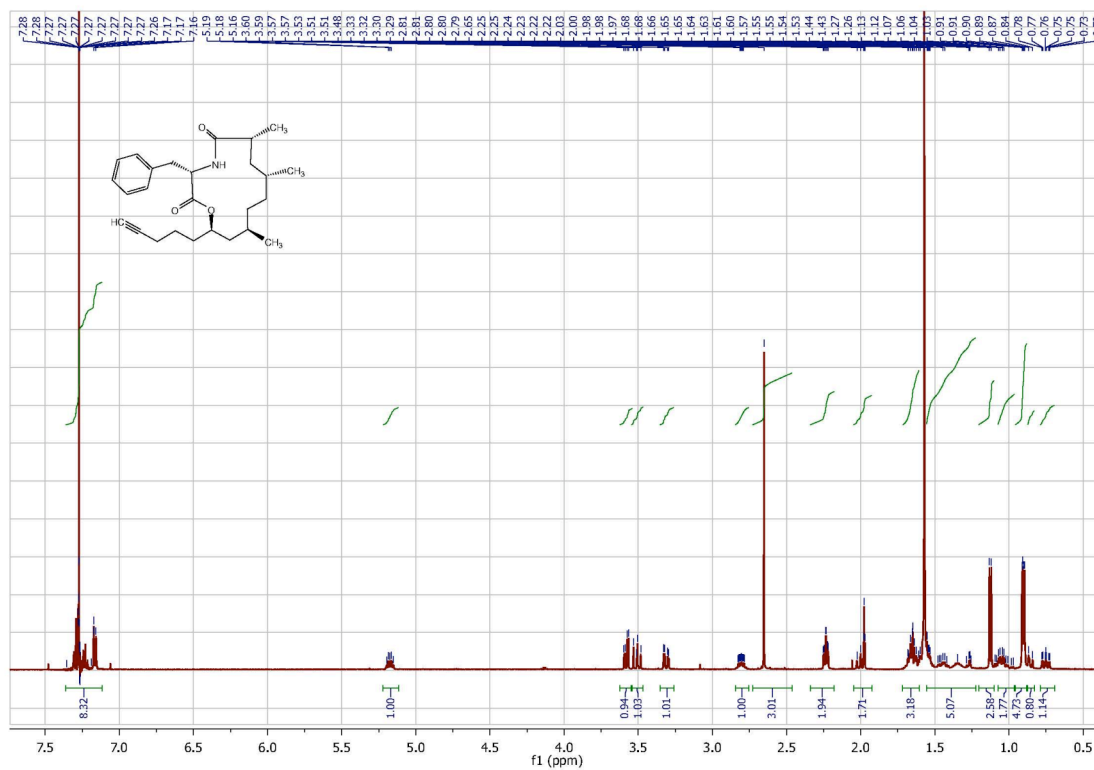
Reported ^1H NMR of (-)-spongidepsin 500 MHz (CD_3OD) *Angew. Chem. Int. Ed.* **2004**,
2148



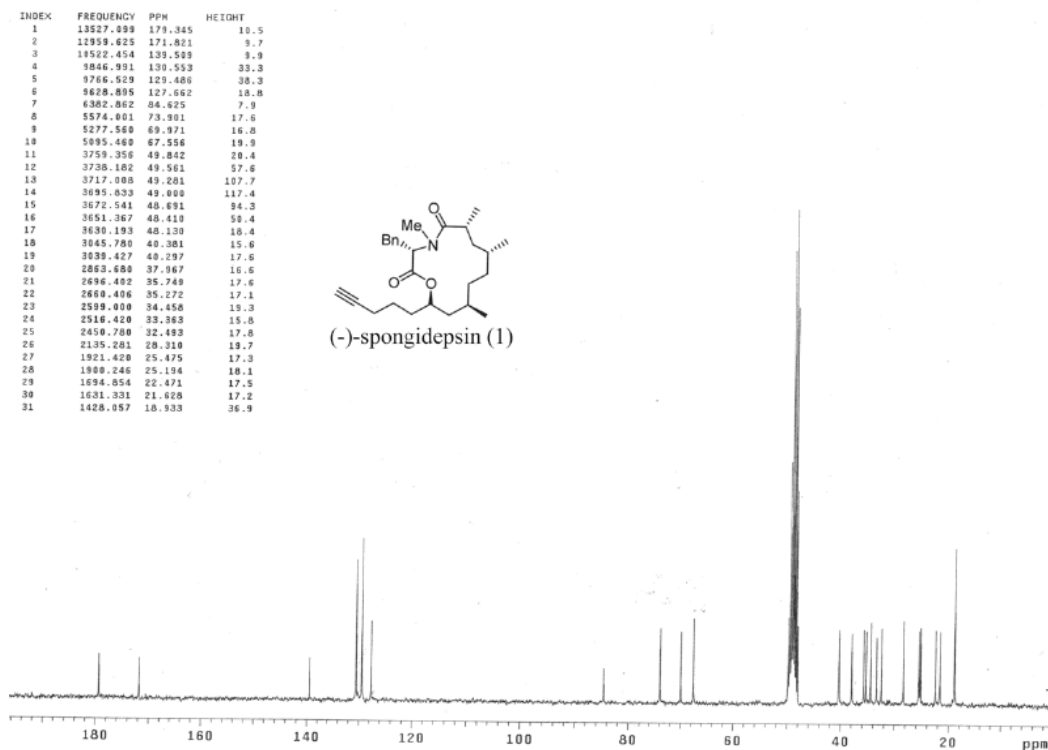
^1H NMR of (-)-spongidepsin synthesized in this work 500 MHz (CD_3OD)



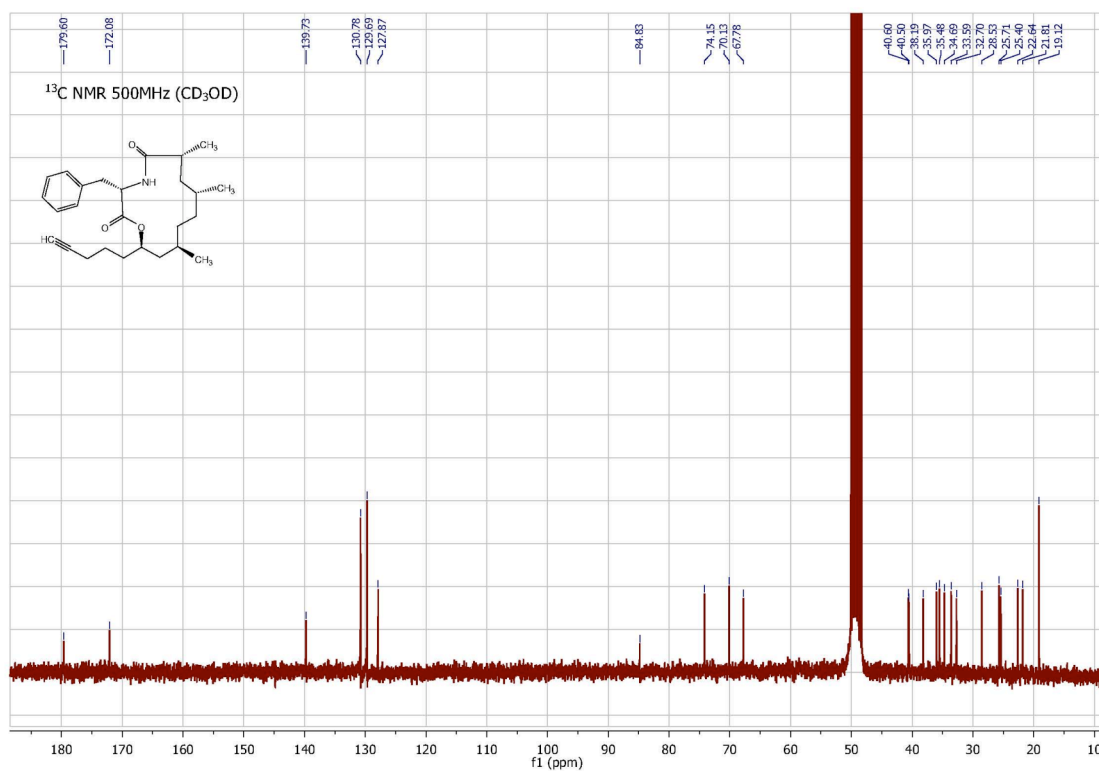
Reported ^1H NMR of (-)-spongidepsin 300 MHz (CDCl_3) *Org. Lett.*, 2007, 2771



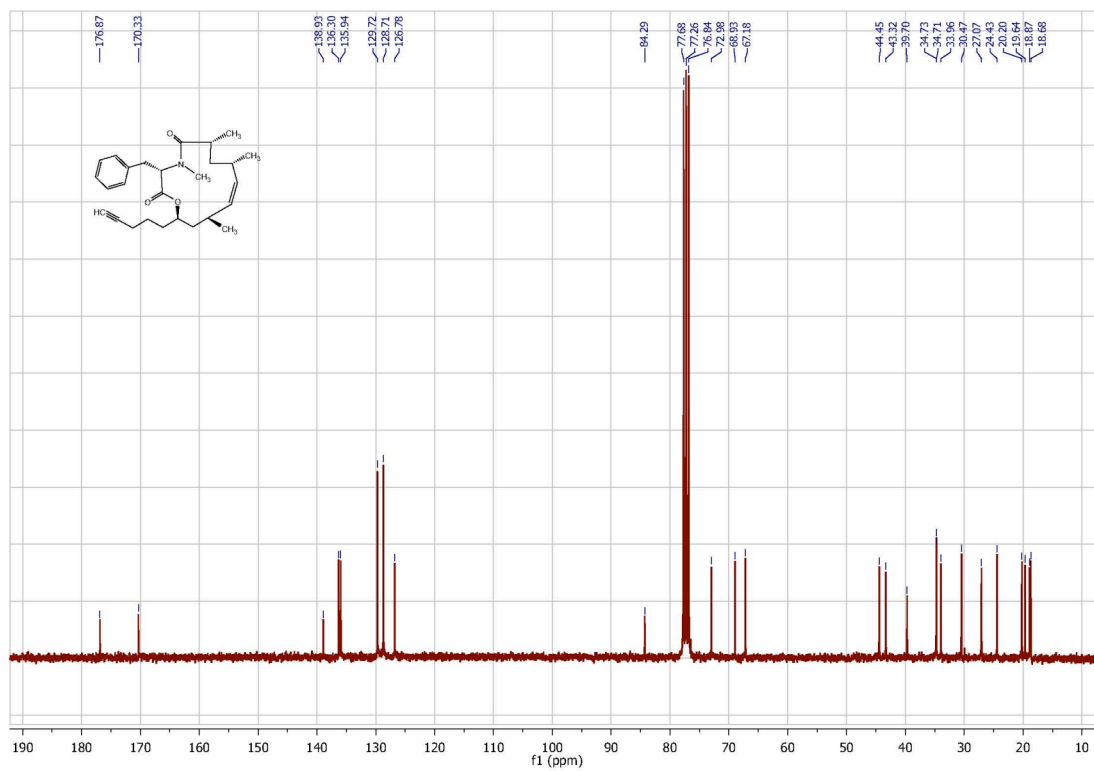
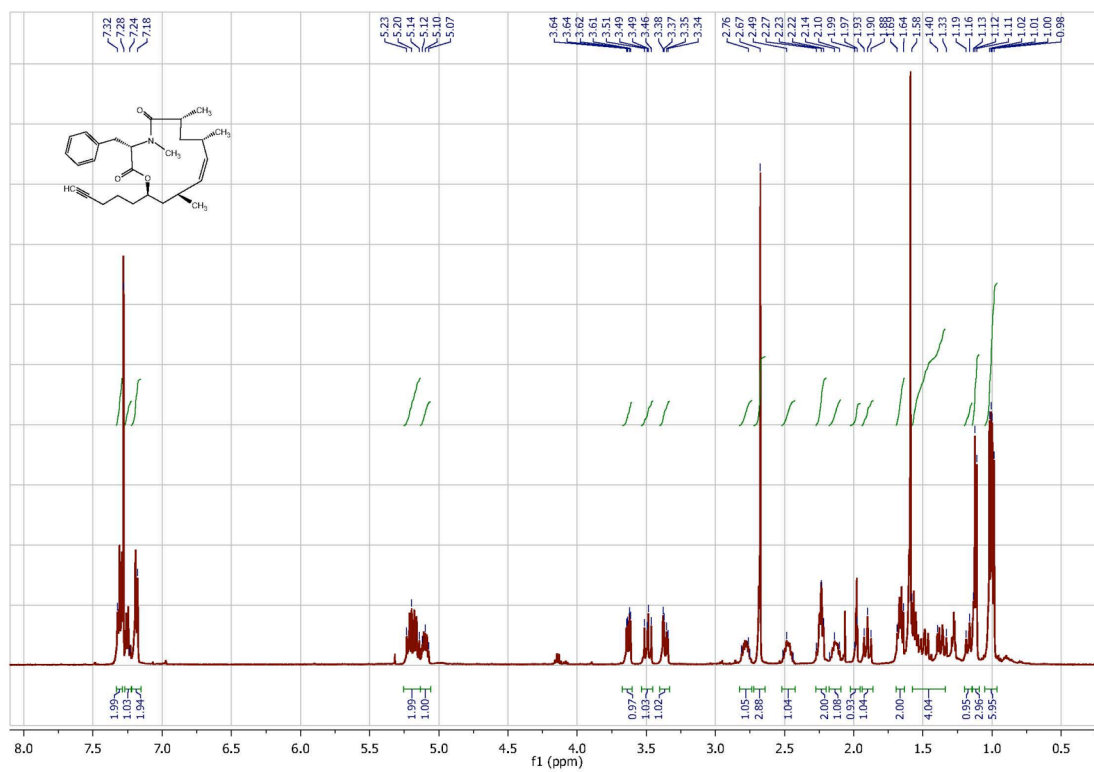
^1H NMR of (-)-spongidepsin synthesized in this work 500 MHz (CDCl_3)

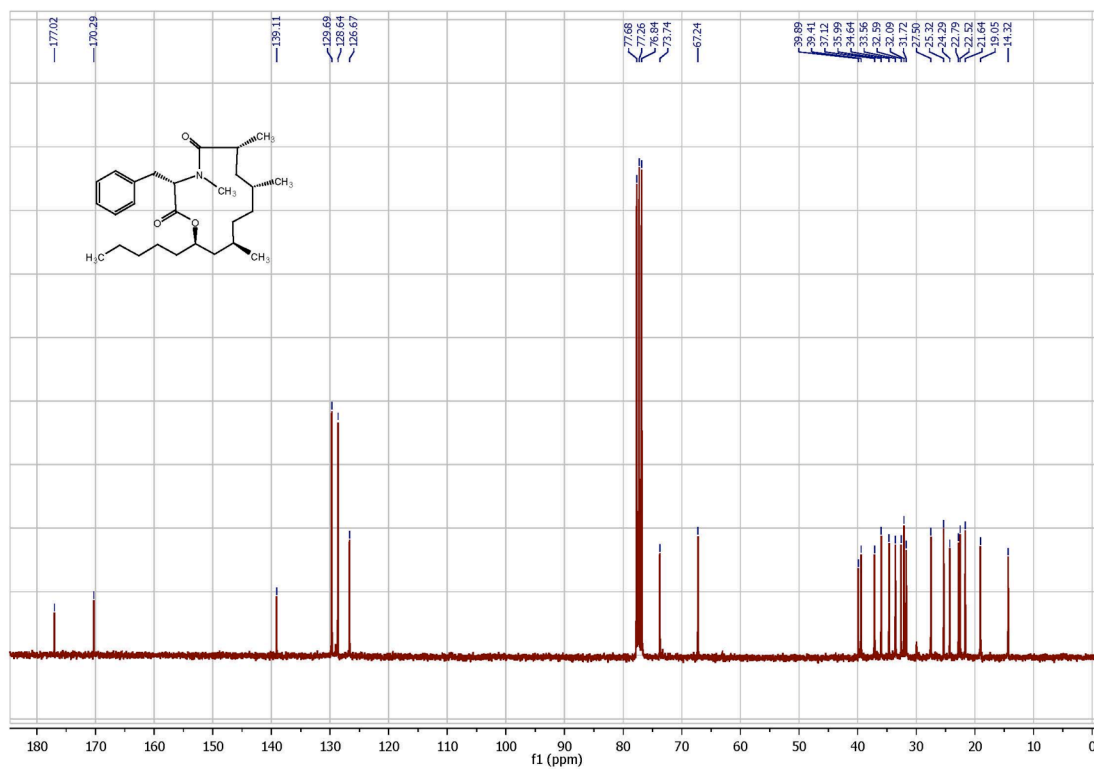
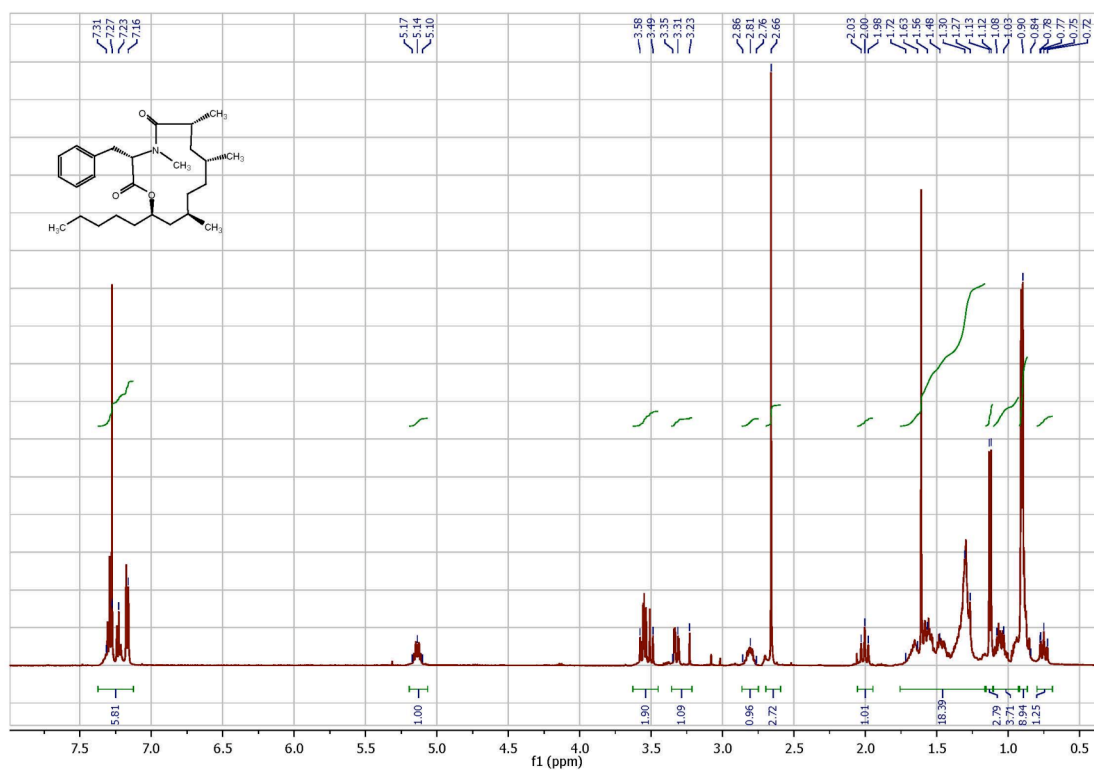


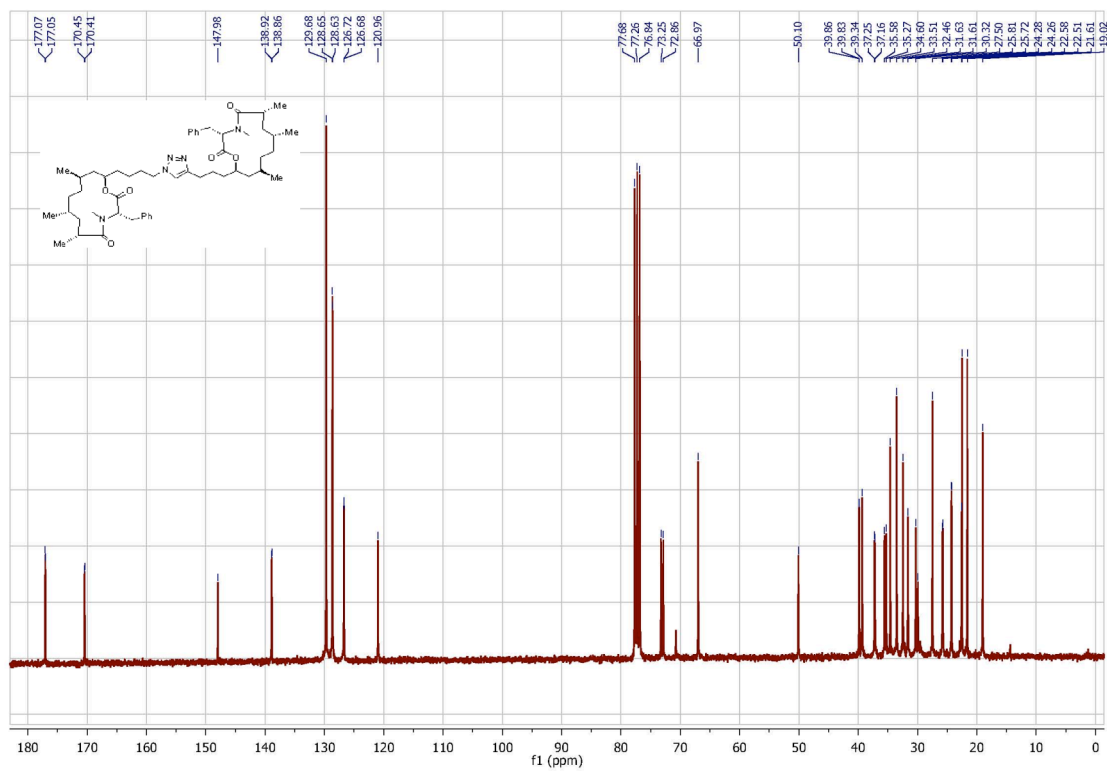
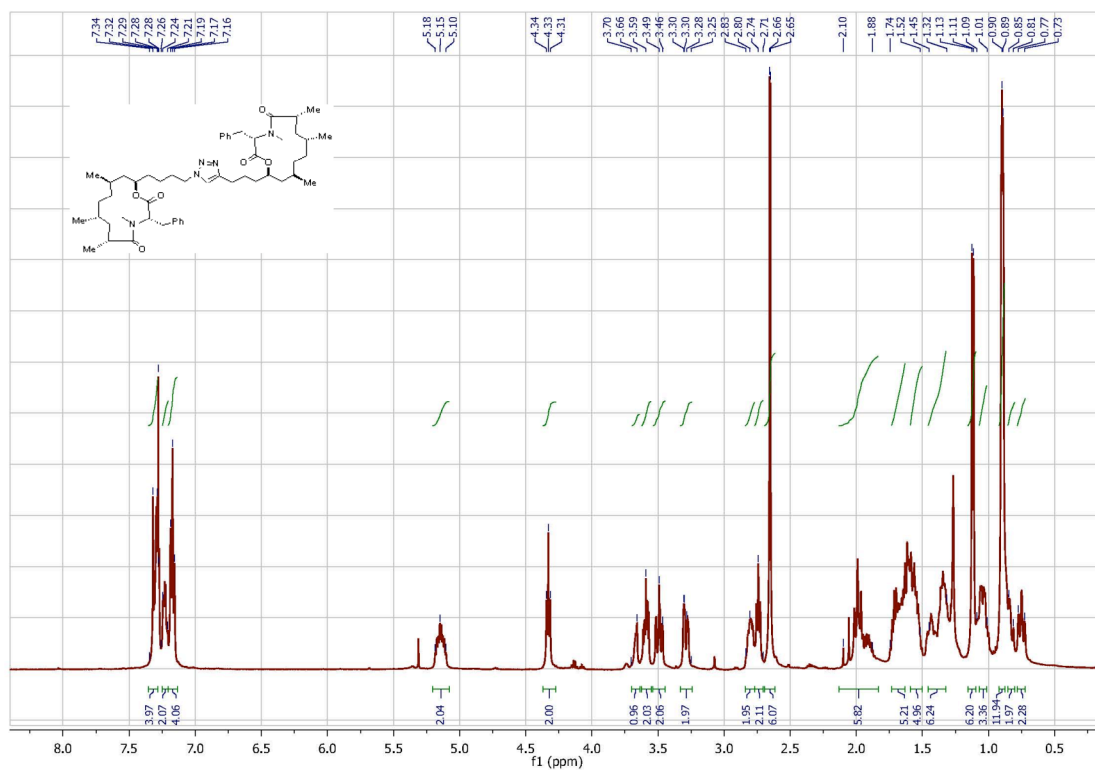
Reported ^{13}C NMR of (-)-spongidepsin 75 MHz (CD_3OD) *Org. Lett.*, **2007**, 2771

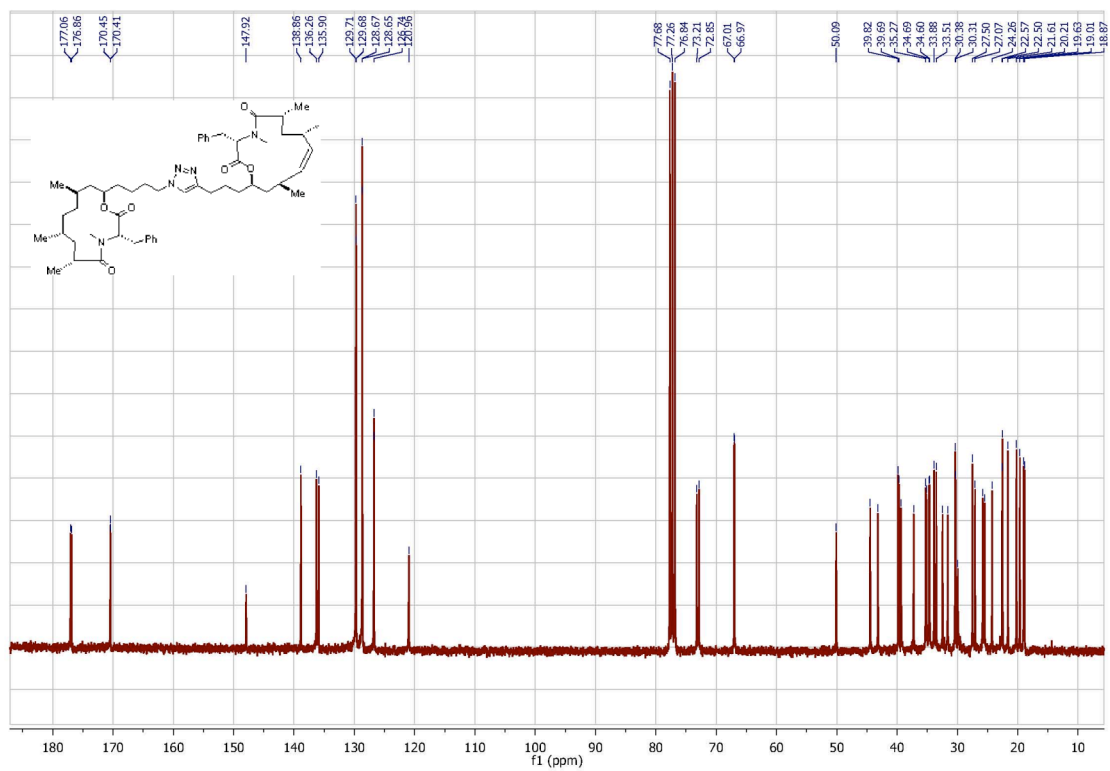
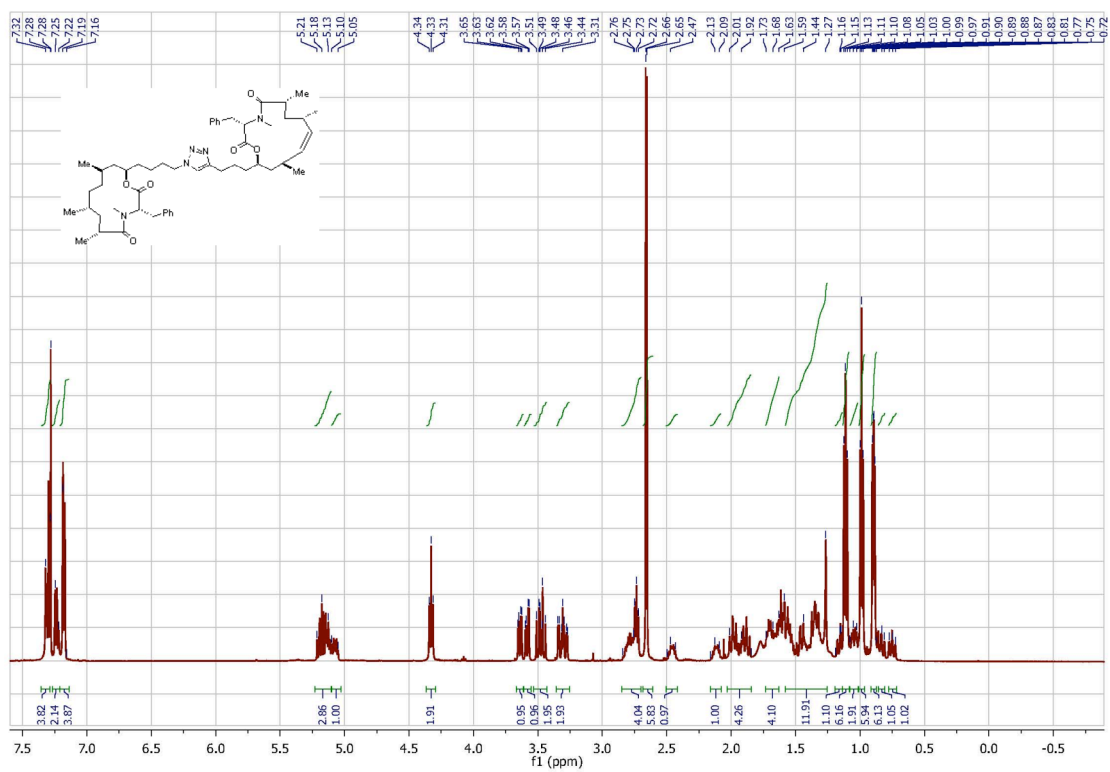


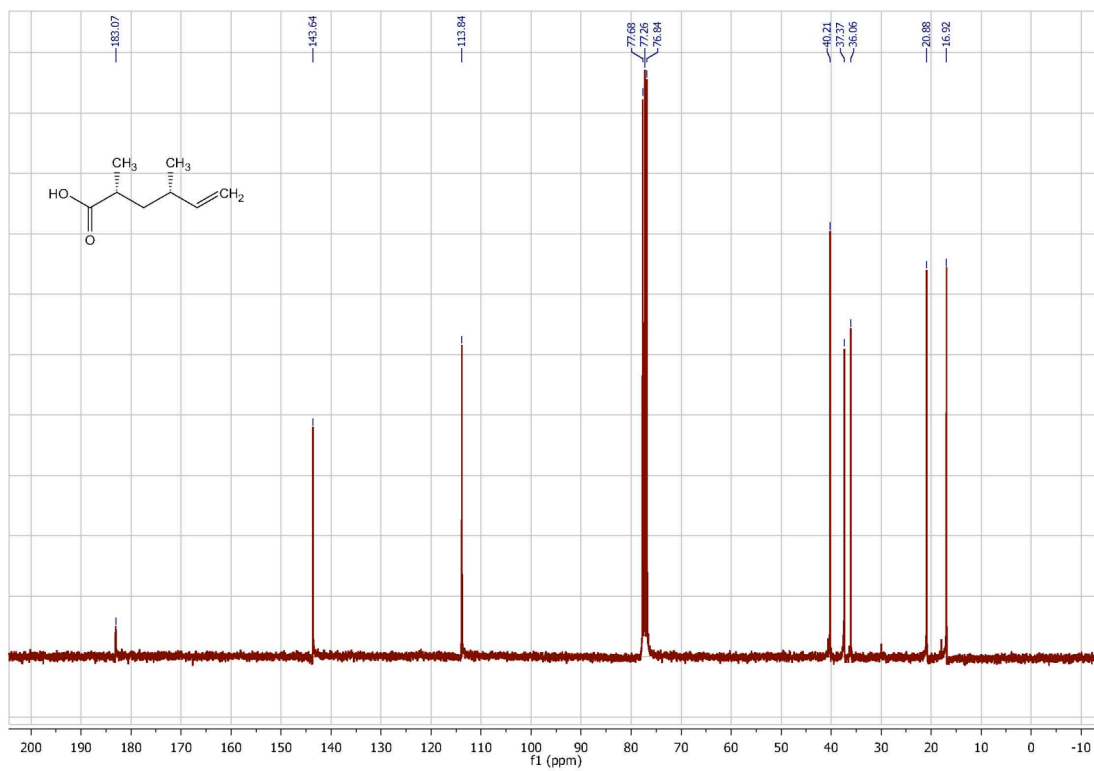
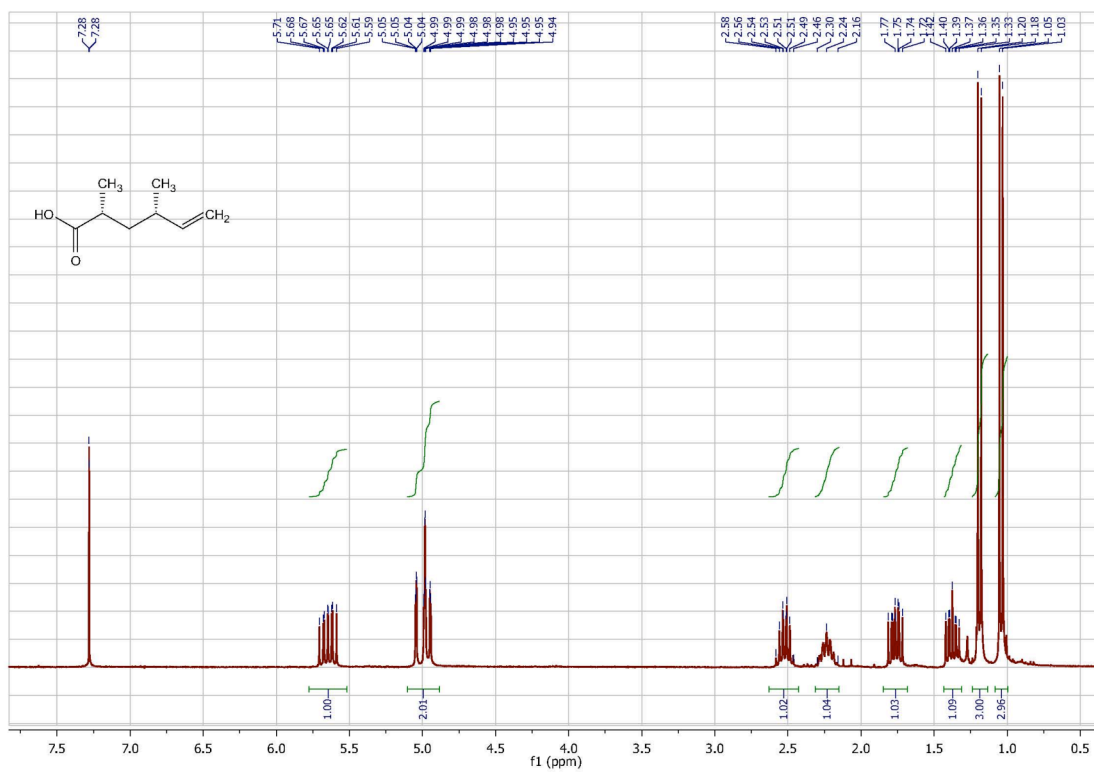
^{13}C NMR of (-)-spongidepsin synthesized in this work 125 MHz (CD_3OD)

^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S12**

^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S13**

^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S15**

¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) of **S16**

^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **S18**

Antiproliferative assay

Human embryonic kidney cells (HEK-293) (3.4×10^4 cells/well, 50 μ L, in Eagle's Minimal Essential Medium (EMEM)) were plated on 96-well plates and allowed to adhere at 37 °C in 5% CO₂ and 95% air for 2 h. Thereafter, the cells were treated with 50 μ L aliquot of each test compounds (Spongidepsin **1**, **15**, **16**, **18** and **19**) in EMEM + 4% Fetal Bovine Serum (FBS) at different concentrations, ranging from 100 nM to 20 μ M. The final concentration of FBS was 2%. The cells were then incubated for 72 h at 37 °C.

The cells' viability was assessed through an MTT conversion assay. Briefly, 25 μ L of MTT (5 mg/mL, in Hank's balanced salt solution, HBSS) were added and the cells were incubated for an additional 2.5 h. Thereafter, the cells were lysed and the dark blue crystals solubilized with 100 μ L of an aqueous solution containing 35 % (v/v) N,N-dimethylformamide, 15 % (v/v) glacial acetic acid, 15% (w/v) SDS with an adjusted pH of 3.8.

The optical density (OD) of each well (at 570 nm) was measured with a BioTek Synergy 4 Microplate Reader. The viability of each cell line in response to the treatment with tested compounds was calculated as: % dead cells = $100 - (\text{OD treated} / \text{OD control}) \times 100$. The results obtained in the antiproliferative assay for (-)-Spongidepsin **1** and the derivatives synthesized herein, expressed as an IC₅₀ value (μ M), are:

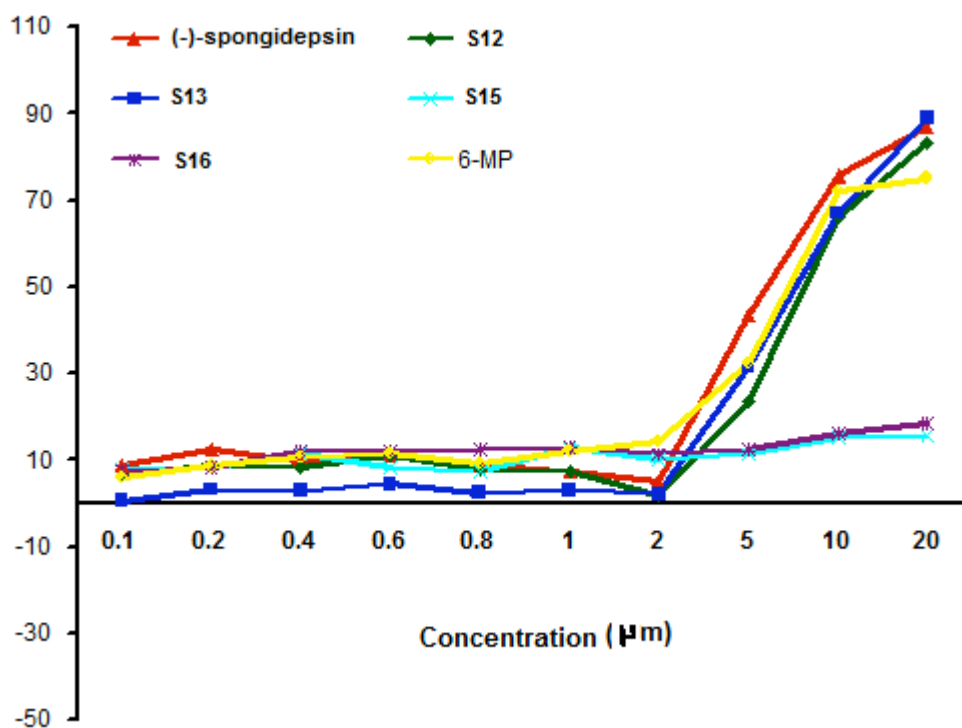


Figure C-1. Anti-proliferation assay on HEK 293 cells treated with (-)-spongidepsin and the derivatives prepared herein. Assay were run for 3 days at 37 °C in EMEM+2% FBS.

Table C-2. In vitro antiproliferative activity of **(-)-spongidepsin** and derivatives

	HEK 293 (μM)
Spongidepsin 1	5.68 (0.66) ^a
15	8.27
16	7.32
18	<i>non cytotoxic</i>
19	<i>non cytotoxic</i>
6-MP	7.45 (0.007) ^a

^a Literature data.⁸

The IC₅₀ value is the concentration of compound that affords 50% reduction in cell growth (after 3 day incubation). HEK-293 is a human epithelial kidney cell line.

The cytotoxicity data in the literature comes from a TL paper (reference 9). We were curious about the difference we were getting, and emailed the authors about it several times: they did not reply. In the paper we do not want to make an issue about just how cytotoxic compound **(-)-spongidepsin** is. It is cytotoxic, and our data (which is hard to screw up in repeated side-by-side assays) shows it is about as much as 6-mercaptopurine. Also the *relative* cytotoxicity of **(-)-spongidepsin** and its analogs is clear here. Again, this is hard to screw up in repeated side-by-side assays; hence we are quite confident of the data shown.

Moreover, we did a literature survey of published cytotoxicity values for 6-mercaptopurine on HEK cells (the ones in the paper). Ref 9 quotes an IC₅₀ of 0.007 μM , and we found 7.5 μM . The three reports from three different groups that we found quote IC₅₀ values of 1.1⁹, 1.7¹⁰, and 5.2¹¹ μM , *ie* about the same as ours (within exp error) and about 100X greater than ref 9.

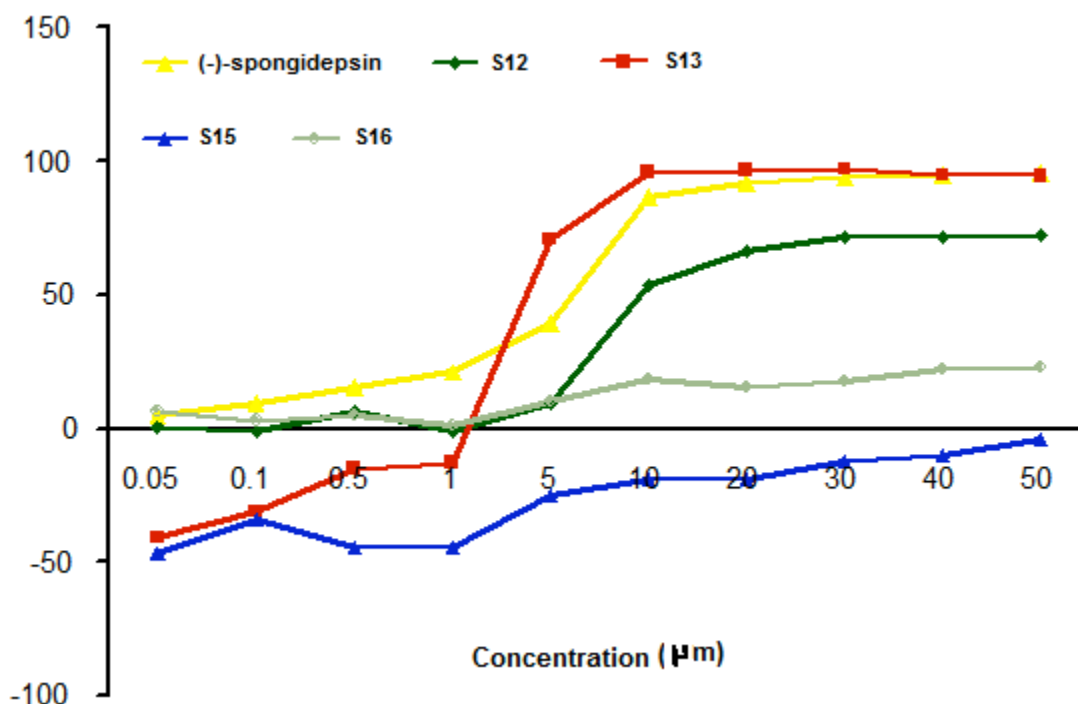


Figure C-2. Anti-proliferation assay on Panc-1 cells treated with Spongidepsin and the derivatives prepared herein. Assay were run for 3 days at 37 °C in PFHM-II medium (protein and serum free medium).

¹ Grise, C. M.; Tessier, G.; Barriault, L. *Org. Lett.* **2007**, *9*, 1545.

² Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

³ Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.

⁴ (a) Chen, J.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 2148. (b) Ghosh, A. K.; Xu, X. *Org. Lett.* **2004**, *6*, 2055. (c) Ferrié, L.; Reymond, S.; Capdevielle, P.; Cossy, J. *Org. Lett.* **2006**, *8*, 3441. (d) Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771.

⁵ Zhou, J.; Burgess, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 1129.

⁶ Smith, A. B. III; Bosanac, T.; Basu, K. *J. Am. Chem. Soc.* **2009**, *131*, 2348.

⁷ Zhu, G.; Negishi, E. *Org. Lett.* **2007**, *9*, 2771.

⁸ Grassia, A.; Bruno, I.; Debitus, C.; Marzocco, S.; Pinto A.; Gomez-Paloma, L.; Riccio, R. *Tetrahedron* **2001**, *57*, 6257.

⁹ Saturnino, C.; Napoli, M.; Paolucci, G.; Bortoluzzi, M.; Popolo, A.; Pinto, A.; Longo, P. *Eur. J. Med. Chem.* **2010**, *45*, 4169.

¹⁰ Wolf, C.; Jansen, R.; Yamaguchi, H.; Haas, M.; Wetering, K.; Wijnholds, J.; Beijnen, J.; Borst, P. *Mol. Cancer Ther.*, **2008**, *7*, 3092.

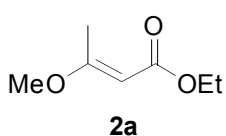
¹¹ Wielinga, P.R.; Reid, G.; Challa, E.E.; Deemiter, L. Van, Haas, M. DE, Mol, C., Kuil, A.J., Groeneveld, E., Schuetz, J.D., Brouwer, C., Abreu, R.A., Wijnholds, J., Beijnen, J.H., Borst, P. *Mol. Pharmacol.* **2002**, *62*, 1321.

APPENDIX D

EXPERIMENTAL DATA FOR CHAPTER IV

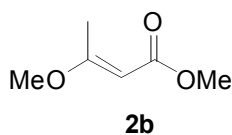
General Procedure for synthesis of vinyl ether esters:

Acetoacetate (50mmol) and orthoformate (50mmol) were added to a 100ml round bottom flask and cooled to 0 °C. Concentrated H₂SO₄ (0.20ml) was then added slowly. The mixture was stirred for 36h at 25 °C. A slight excess of quinoline (0.50ml) was added. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave the corresponding vinyl ether esters as colorless oils.



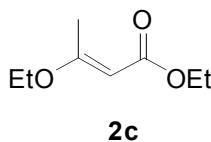
Starting with ethyl acetoacetate and trimethyl orthoformate (adding 1eq. anhydrous CaCl₂) (74% yield) ^[2]

¹H NMR (300 MHz, CDCl₃) δ 4.93 (1H, s), 4.05 (2H, q, *J* = 7.2 Hz), 3.54 (3H, s), 2.20 (3H, s), 1.18 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 167.8, 90.9, 59.2, 55.3, 18.8, 14.4.



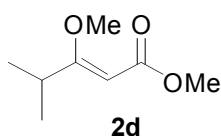
Starting with methyl acetoacetate and trimethyl orthoformate (65% yield) ^[3]

¹H NMR (300 MHz, CDCl₃) δ 5.04 (1H, s), 3.69 (3H, s), 3.64 (3H, s), 2.31 (3H, s); ¹³C NMR (75 MHz, CDCl₃) δ 173.0, 168.0, 90.3, 55.1, 50.3, 18.6.



Starting with ethyl acetoacetate and triethyl orthoformate (60% yield)

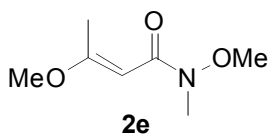
¹H NMR (300 MHz, CDCl₃) δ 5.01 (1H, s), 4.14 (2H, q, *J* = 7.2 Hz), 3.83 (2H, q, *J* = 7.2 Hz), 2.31 (3H, s), 1.35 (3H, t, *J* = 7.2 Hz), 1.28 (3H, t, *J* = 7.2 Hz). ¹³C NMR (75 MHz, CDCl₃) δ 172.5, 168.2, 91.2, 63.89, 59.4, 19.3, 14.6, 14.4. MS (ESI): Exact mass calcd for C₈H₁₅O₃[M+H]⁺ 159.10. Found 159.10.



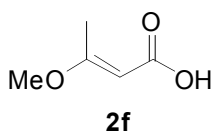
Starting with methyl isobutyrylacetate and trimethyl orthoformate (65% yield) ^[4]

¹H NMR (300 MHz, CDCl₃) δ 4.87 (1H, s), 4.02-3.93 (1H, m), 3.63 (3H, s), 3.59 (3H, s), 1.04 (6H, d, *J* = 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 180.8, 168.1,

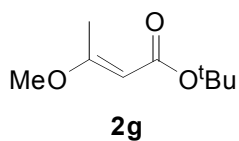
88.6, 55.6, 50.8, 29.3, 19.8. MS (ESI): Exact mass calcd for $C_8H_{15}O_3[M+H]^+$ 159.10. Found 159.10.



To a cooled solution (0 °C) of compound **2b** (0.86 g, 6.6 mmol) in CH_2Cl_2 (30 mL) was added $Me(OMe)NH\cdot HCl$ (1.93 g, 19.8 mmol) followed by dropwise addition of $AlMe_3$ solution (2 M in toluene, 9.9 mL, 19.8 mmol). The resulting mixture was heated to 40°C for 4 h. The reaction was then cooled to 0°C first then was diluted with CH_2Cl_2 (20 mL) and carefully add H_2O (10 mL). Saturated potassium sodium tartrate aqueous solution (40 mL) was then added. The resulting mixture was vigorously stirred for 30 min and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (15:85) gave Wenireb amide **2e** (0.43 g, 41%) as a colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ 5.55 (1H, s), 3.67 (3H, s), 3.64 (3H, s), 3.18 (3H, s), 2.29 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 169.2, 88.8, 61.4, 55.3, 32.6, 19.1. MS (ESI): Exact mass calcd for $C_7H_{14}NO_3 [M+H]^+$ 160.10. Found 160.10.



To compound **2b** (3.0 g, 23 mmol) in a 100 mL round bottom flask was added a solution of KOH (1.3 g, 23 mmol) in H_2O (80 mL). The mixture was stirred at 25 °C for 1d until the solution became homogeneous. Extracted with Et_2O (50 mL) and the aqueous layer was acidified to pH 2 and then extracted with Et_2O (3×30 mL) again. The latter ether extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by recrystallization (Hexanes) gave desired acid **2f** (1.7 g, 65%) as a white solid. 1H NMR (300 MHz, $CDCl_3$) δ 5.05 (1H, s), 3.68 (3H, s), 2.31 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 173.9, 90.7, 55.9, 19.5. MS (ESI): Exact mass calcd for $C_5H_7O_3[M-H]^+$ 115.04. Found 115.02.

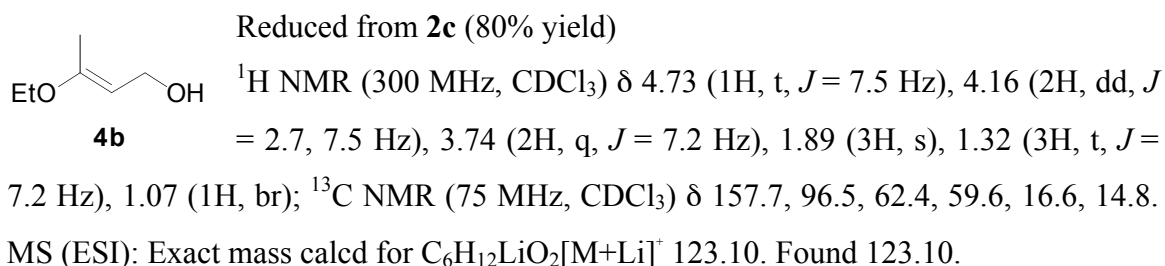
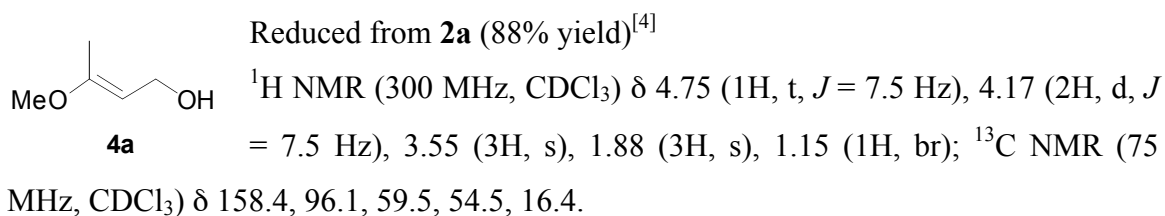


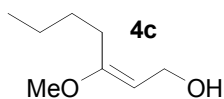
To a cooled solution (0 °C) of compound **2f** (0.45 g, 3.8 mmol) in CH_2Cl_2 (3.8 mL) was added t-butyl 2,2,2-trichloroacetimidate (1.70 g, 7.6 mmol) in cyclohexane (15.2 mL) followed by dropwise

addition of $\text{BF}_3 \cdot \text{OEt}_2$ (0.076 ml). The mixture was stirred at room temperature for 8h. Diluted with CH_2Cl_2 (10 mL) and $\text{NaHCO}_3(\text{s})$ (20 mL) was carefully added at 0 °C. The aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (5:95) gave ester **2g** (0.33 g, 50%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 4.96 (1H, s), 3.62 (3H, s), 2.27 (3H, s), 1.49 (9H, s); ^{13}C NMR (75 MHz, CDCl_3) δ 172.2, 167.7, 92.8, 79.4, 55.5, 28.6, 19.0. MS (CI): Exact mass calcd for $\text{C}_9\text{H}_{16}\text{O}_3$ $[\text{M}+\text{H}]^+$ 173.1. Found 173.2.

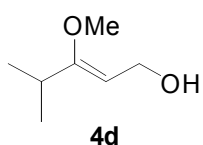
General Procedure for synthesis of vinyl ether alcohols:

To a cooled solution (0 °C) of vinyl ether ester (5 mmol) in CH_2Cl_2 was added dropwise a solution of DIBAL-H (1 M in Hexanes, 15mmol). Stirring was continued for 1 h and then the reaction was cooled to 0 °C and quenched by slow addition of MeOH. The reaction was diluted with CH_2Cl_2 and a saturated aqueous solution of potassium sodium tartrate was added. The resulting mixture was vigorously stirred for 30 min and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 . The combined organic extracts were dried (K_2CO_3) and concentrated *in vacuo*. Purification by flash column chromatography on Al_2O_3 , eluting with EtOAc/hexanes (30:70) gave the corresponding vinyl ether alcohols as colorless oils.

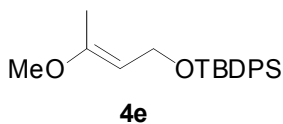




Methyl 3-oxoheptanoate (20mmol) and trimethyl orthoformate (20mmol) were added to a 100ml round bottom flask and cooled to 0 °C. Concentrated H₂SO₄ (0.1ml) was then added slowly. The mixture was stirred for 36h at 25 °C. A slight excess of quinoline (0.50ml) was added. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave the corresponding vinyl ether esters as colorless oils. Directly reducing the ester gave the **4c** as colorless oil (51% yield for 2 steps). ¹H NMR (300 MHz, CDCl₃) δ 4.72 (1H, t, *J* = 7.5 Hz), 4.17 (2H, d, *J* = 7.5 Hz), 3.54 (3H, s), 2.22 (2H, t, *J* = 7.5 Hz), 1.64-1.46 (2H, m), 1.36-1.29 (2H, m), 1.29 (1H, br), 0.92 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 96.0, 59.3, 54.5, 30.5, 30.3, 22.7, 14.2. MS (CI): Exact mass calcd for C₈H₁₇O₂[M+H]⁺ 145.0. Found 145.1.

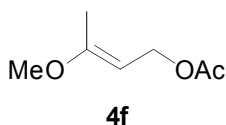


Reduced from **2d** (78% yield)^[5]
¹H NMR (300 MHz, CDCl₃) δ 4.53 (1H, t, *J* = 7.8 Hz), 4.10 (2H, d, *J* = 7.8 Hz), 3.45 (3H, s), 2.86-2.77 (1H, m), 2.10 (1H, br), 1.00 (6H, d, *J* = 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 165.5, 94.1, 58.3, 54.4, 28.5, 20.5. MS (ESI): Exact mass calcd for C₇H₁₅O₂[M+H]⁺ 131.11. Found 131.20.



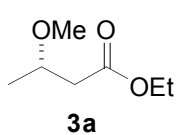
To a cooled solution of compound **4a** (0.21 g, 2.0 mmol) and imidazole (0.17 g, 2.5 mmol) in CH₂Cl₂ (10 mL) was added TBDPSCl (0.63 g, 2.3 mmol). The mixture was stirred at 25 °C for 1 h, then the reaction was quenched by addition of saturated NaHCO₃ aqueous solution (5 mL). The layers were separated and aqueous layer was extracted with CH₂Cl₂ (3×10 mL). The combined organic extracts were dried (K₂CO₃) and concentrated *in vacuo*. Purification by flash chromatography on basic Al₂O₃ eluting with EtOAc/Hexanes (10:90) gave the desired product **4e** (0.53 g, 75%) as a colorless oil. ¹H NMR (300 MHz, CDCl₃) δ 7.74-7.71 (4H, m), 7.43-7.40 (6H, m), 4.63 (1H, t, *J* = 7.2 Hz), 4.24 (2H, d, *J* = 7.2 Hz), 3.48 (3H, s), 1.64 (3H, s), 1.07 (9H, s); ¹³C NMR (75 MHz, CDCl₃) δ 156.4,

136.0, 134.5, 129.8, 127.9, 96.8, 61.2, 54.4, 27.2, 19.5, 16.5. MS (CI): calcd for $C_{21}H_{29}O_2Si$ $[M+H]^+$ 341.2. Found 341.3.



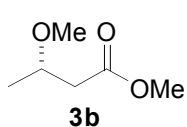
To a cooled solution of compound **4a** (0.32 g, 3.0 mmol) and DMAP (36 mg, 0.30 mmol) in CH_2Cl_2 (12 mL) was added Ac_2O (0.43 mL, 4.5 mmol) and Et_3N (0.63 mL, 4.5 mmol) sequentially. The reaction mixture was stirred at 25 °C for 30 min, then the reaction was quenched by addition of saturated NH_4Cl aqueous solution (5 mL). The layers were separated and aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed by water, saturated brine and then dried by Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography on basic Al_2O_3 eluting with EtOAc/Hexanes (5:95) gave the desired product **4f** (0.31 g, 72%) as a colorless oil. 1H NMR (300 MHz, $CDCl_3$) δ 4.69–4.59 (2H, m), 4.64 (1H, s), 3.55 (3H, s), 2.06 (3H, s), 1.89 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 160.4, 91.3, 62.0, 54.7, 21.4, 16.6. MS (CI): calcd for $C_7H_{13}O_3$ $[M+H]^+$ 145.1. Found 145.0.

General catalytic hydrogenation conditions: the corresponding alkene was dissolved in CH_2Cl_2 (0.5 M) and the Iridium catalyst (L-cat) (1 mol %) was then added. The resulting solution was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was flushed with hydrogen for 1 min without stirring. The mixture was then stirred at 700 rpm under 50 bar H_2 . After 48h (for esters and its derivatives) or 12 h (for alcohols and its derivatives^[6]), the bomb was vented and the solvent evaporated. The crude product was passed through a silica plug (EtOAc/hexanes =3:7). The enantiomeric ratio of the crude material was then measured through chiral capillary GC analysis using β - or a γ -CD column^[7] (carrier gas: helium; column pressure: 18.21 Psi; gas flow rate: 1.6 mL/min; gradient temperature: 5 °C/min: 60 °C hold time: 10 min, 120 °C, 15 min).

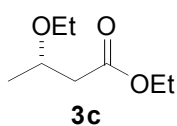


1H NMR (300 MHz, $CDCl_3$) δ 4.16 (2H, q, $J = 7.2$ Hz), 3.82–3.76 (1H, m), 3.35 (3H, s), 2.58 (1H, dd, $J = 7.2, 15$ Hz), 2.37 (1H, dd, $J = 6.0, 15$ Hz), 1.28 (3H, t, $J = 7.2$ Hz), 1.22 (3H, d, $J = 6.3$ Hz); ^{13}C NMR (75

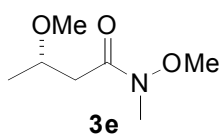
MHz, CDCl₃) δ 171.3, 73.9, 61.7, 56.3, 35.7, 21.2, 19.2. MS (CI): calcd for C₇H₁₅O₃ [M+H]⁺ 147.1. Found 147.0.



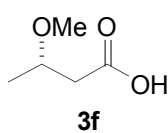
¹H NMR (300 MHz, CDCl₃) δ 3.75-3.68 (1H, m), 3.63 (3H, s), 3.28 (3H, s), 2.52 (1H, dd, *J* = 7.2, 15 Hz), 2.32 (1H, dd, *J* = 5.7, 15 Hz), 1.15 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 172.0, 73.7, 56.4, 51.7, 41.6, 19.2. MS (ESI): calcd for C₆H₁₃O₃ [M+H]⁺ 133.09. Found 133.09.



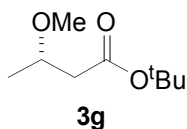
¹H NMR (300 MHz, CDCl₃) δ 4.15 (2H, q, *J* = 7.2 Hz), 3.89-3.86 (1H, m), 3.60-3.42 (2H, m), 2.58 (1H, dd, *J* = 7.2, 15 Hz), 2.36 (1H, dd, *J* = 6.0, 15 Hz), 1.27 (3H, t, *J* = 7.2 Hz), 1.21 (3H, d, *J* = 6.3 Hz), 1.18 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 72.2, 64.3, 60.6, 42.4, 20.2, 15.7, 14.5. MS (ESI): calcd for C₈H₁₆LiO₃[M+Li]⁺ 167.13. Found 167.10.



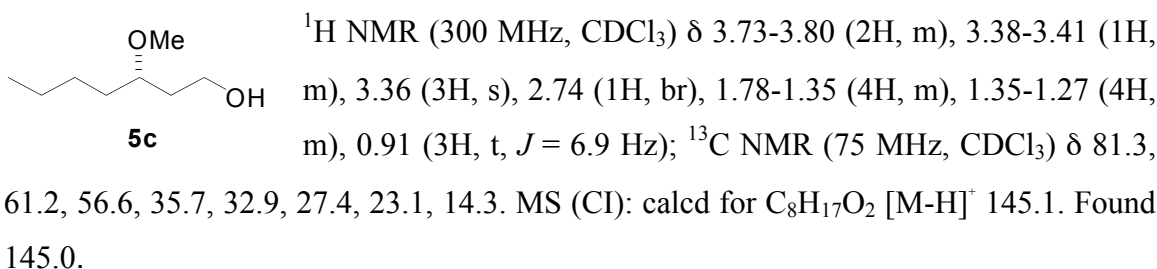
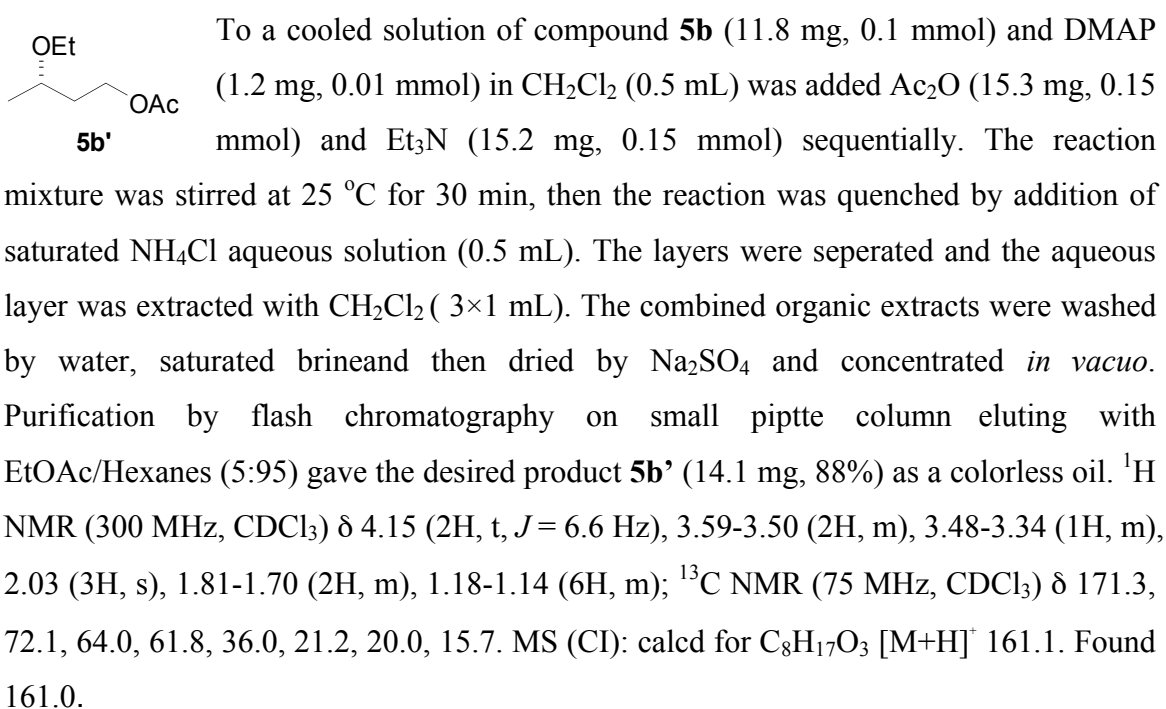
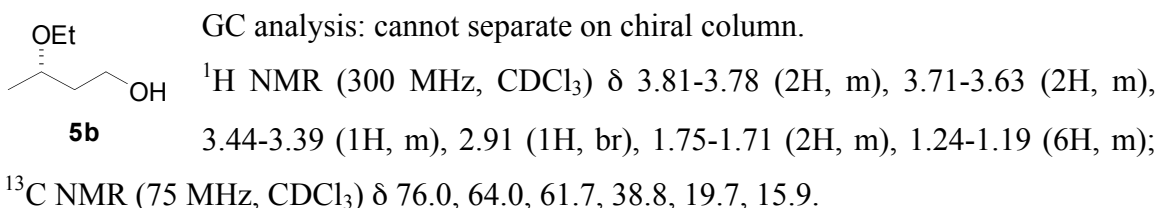
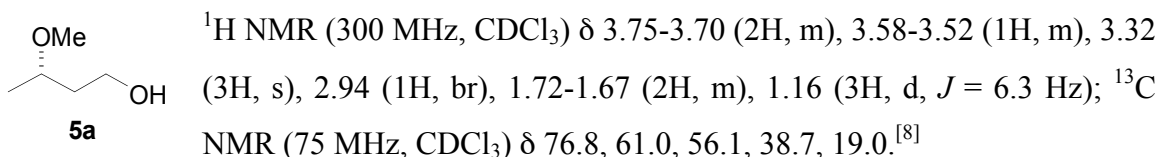
¹H NMR (300 MHz, CDCl₃) δ 3.89-3.83 (1H, m), 3.70 (3H, s), 3.35 (3H, s), 3.20 (3H, s), 2.82 (1H, dd, *J* = 6.9, 15.6 Hz), 2.38 (1H, dd, *J* = 5.7, 15.6 Hz), 1.23 (3H, d, *J* = 6.0 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 172.6, 73.8, 61.5, 56.2, 39.2, 32.2, 19.6. MS (ESI): calcd for C₇H₁₆NO₃[M+H]⁺ 162.11. Found 161.95.

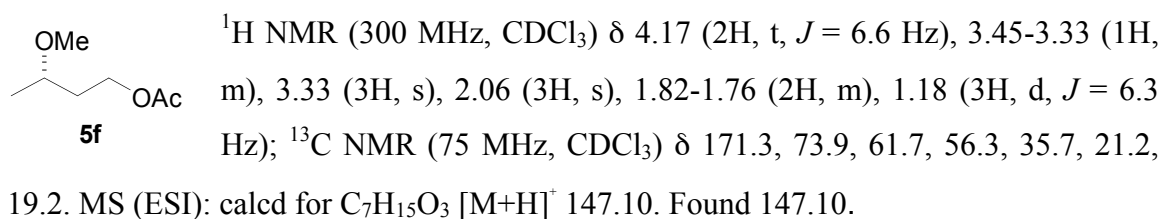
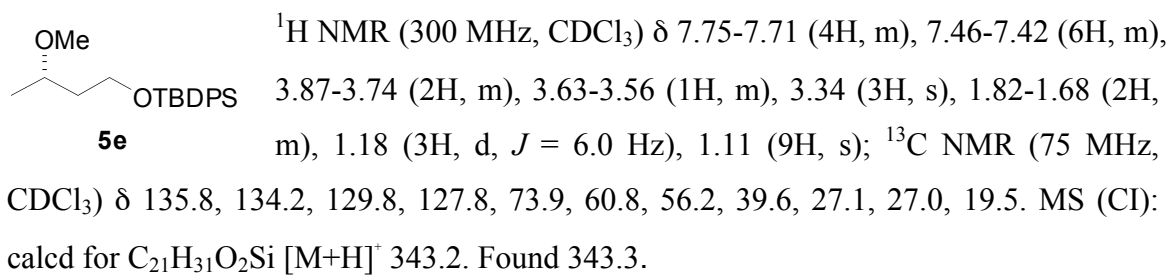
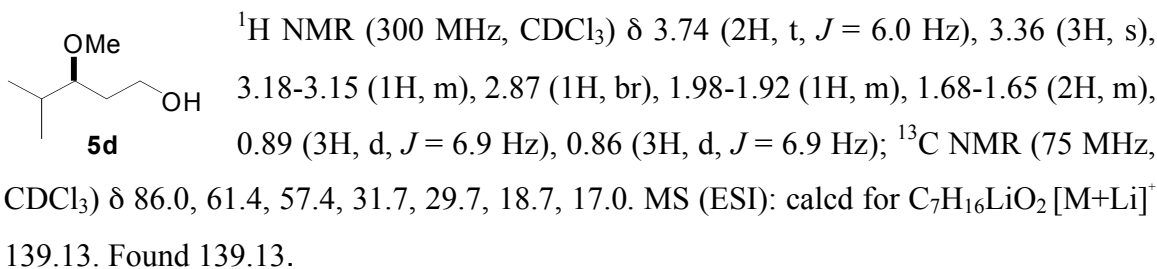


¹H NMR (300 MHz, CDCl₃) δ 3.84-3.78 (1H, m), 3.40 (3H, s), 2.65-2.47 (2H, m), 1.26 (3H, d, *J* = 6.3 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 177.0, 73.7, 56.5, 41.6, 19.2. MS (ESI): calcd for C₅H₉O₃[M-H]⁺ 117.06. Found 117.03.



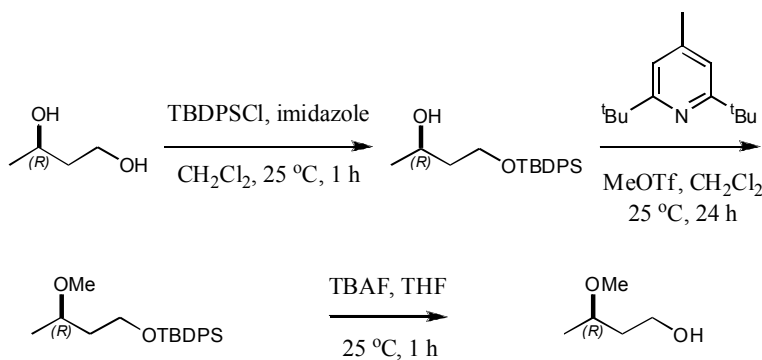
The hydrogenation product **3g** cannot be separated on GC, so directly reduced to alcohol **5a**.



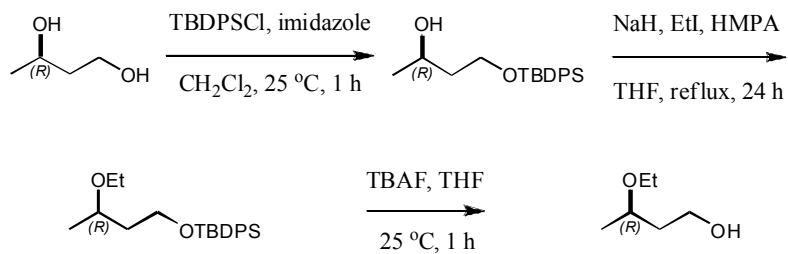


Methods used to determine the absolute chemistry of hydrogenation products

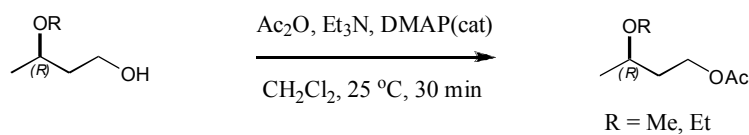
Preparation of enantiomer pure **5a** ^[9]



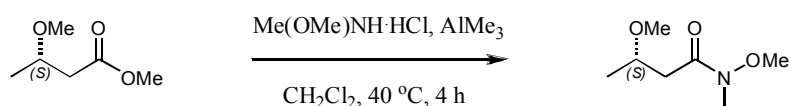
Preparation of enantiomer pure **5b**



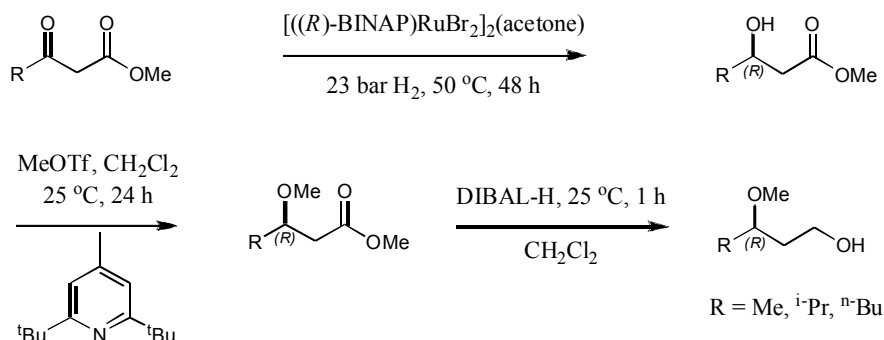
Preparation of enantiomer pure **5f**, **5b'**



Preparation of enantiomer rich **3e**

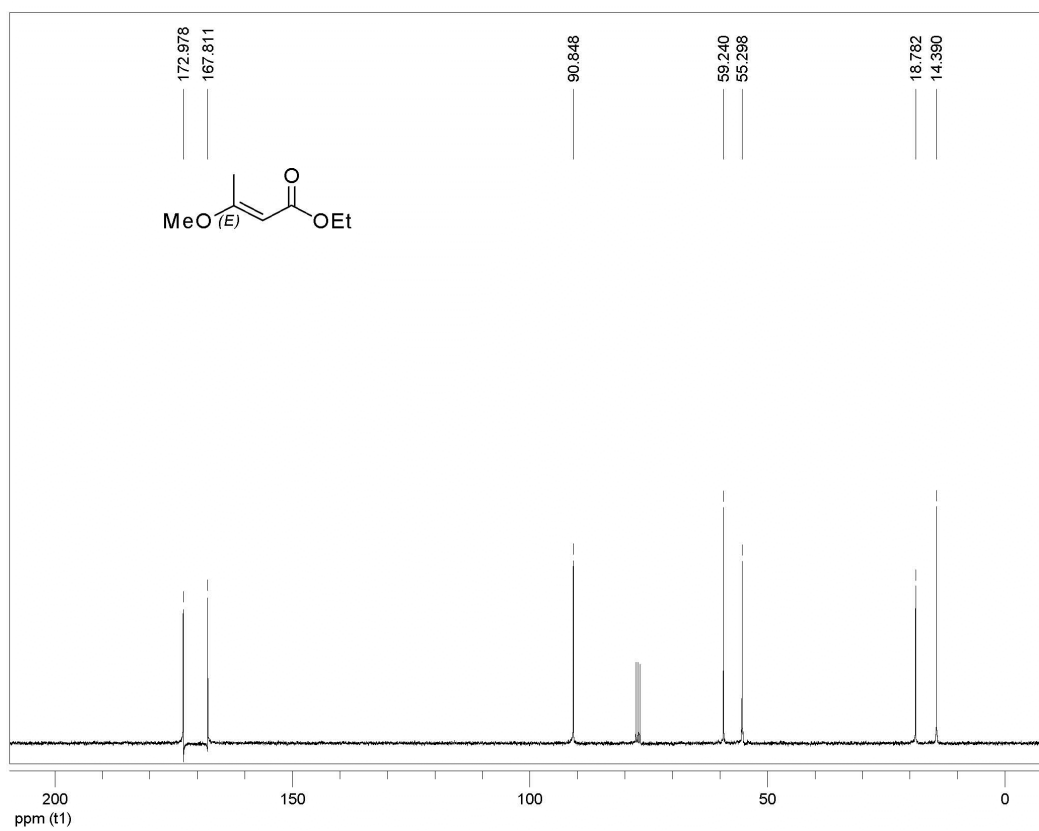
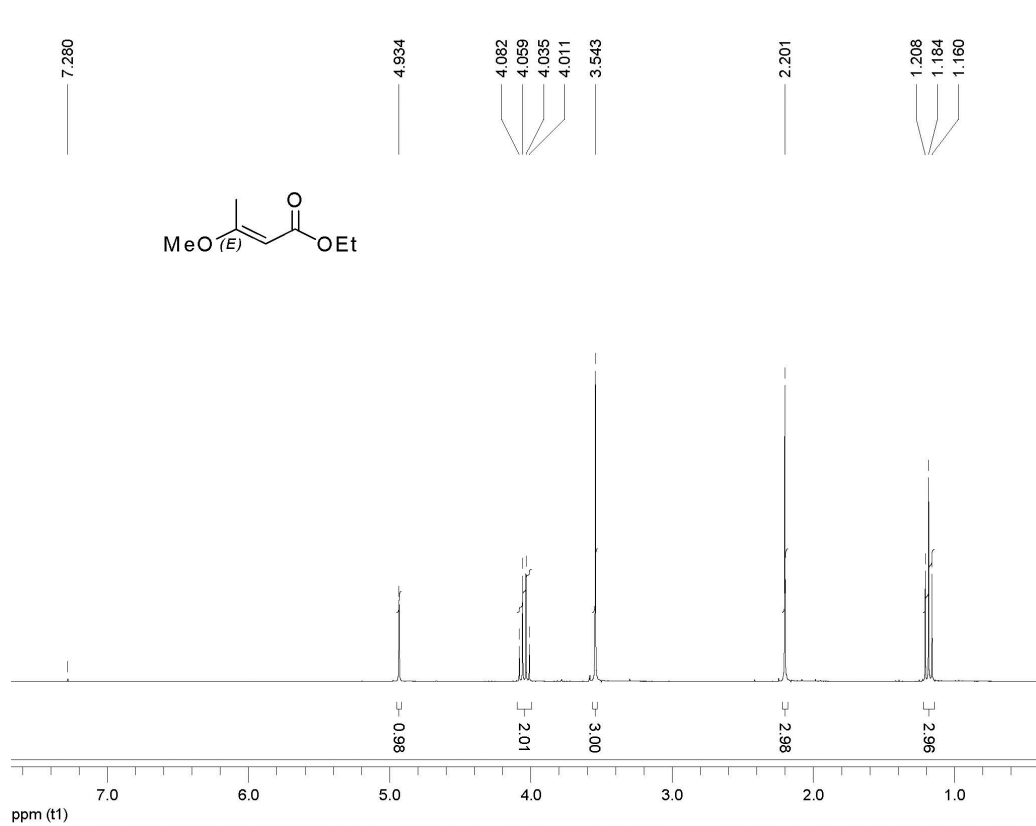


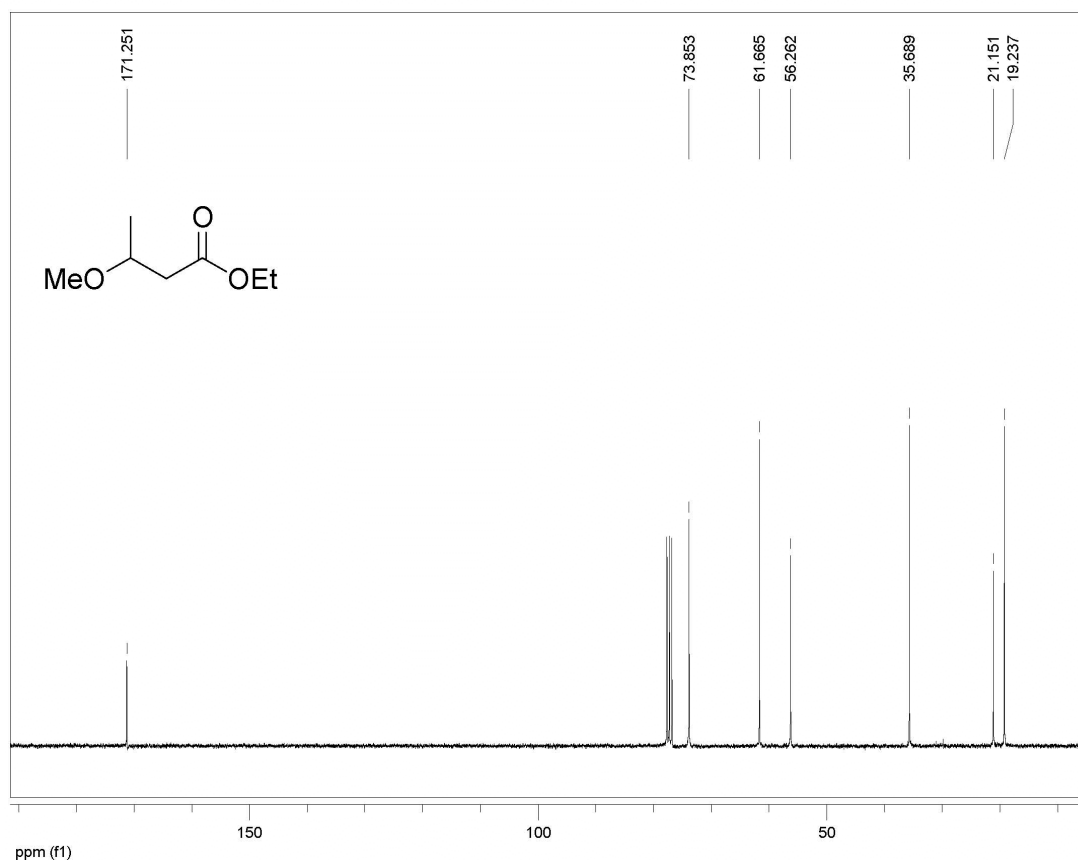
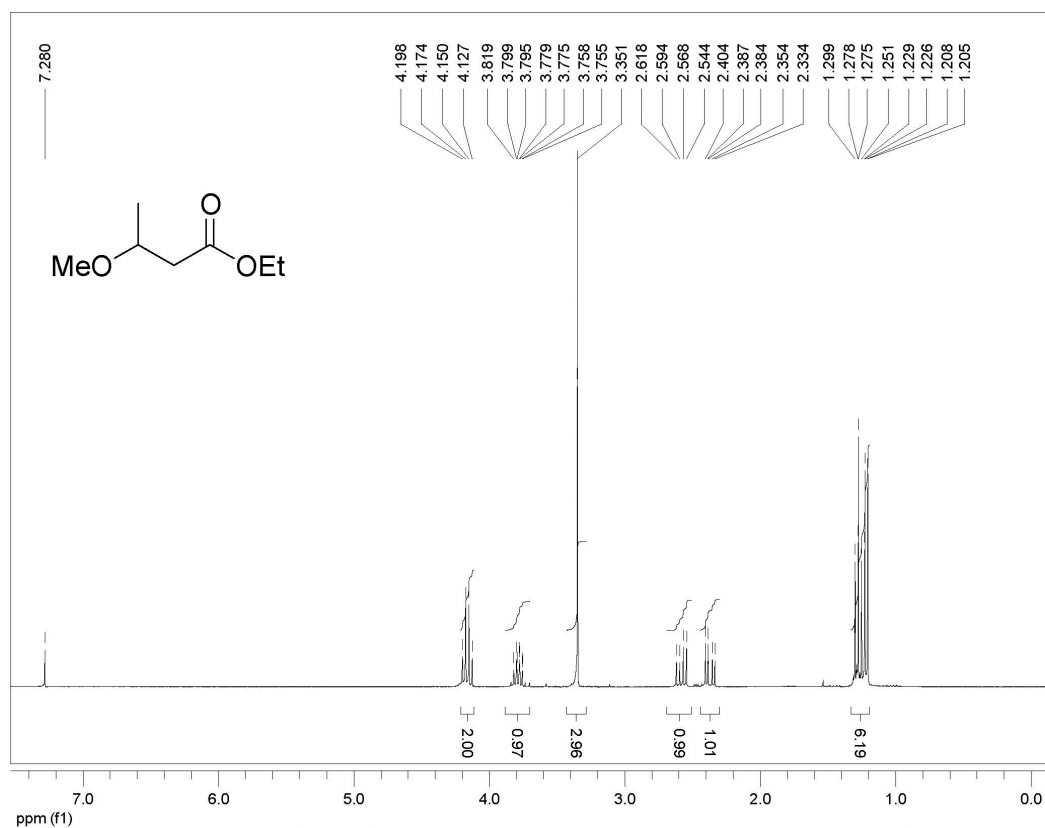
Preparation of enantiomer rich **3b**, **3d**, **5c**, **5d** ^{[9], [10]}

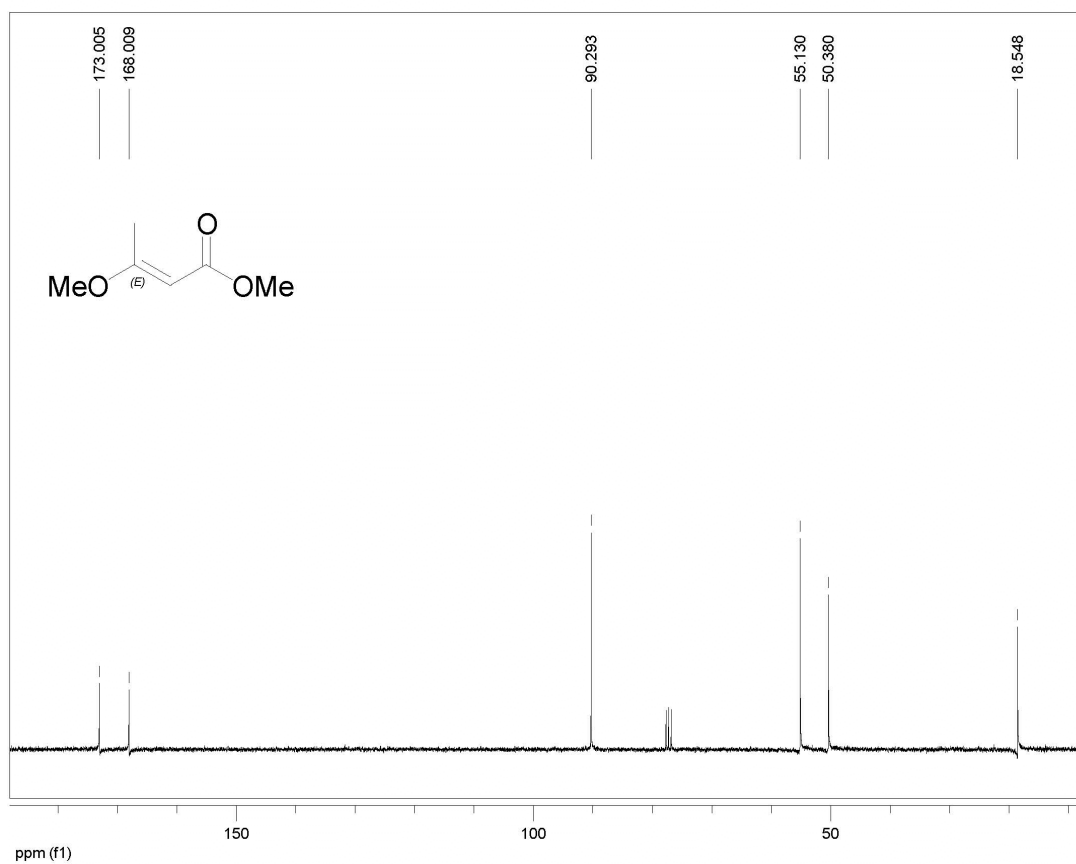
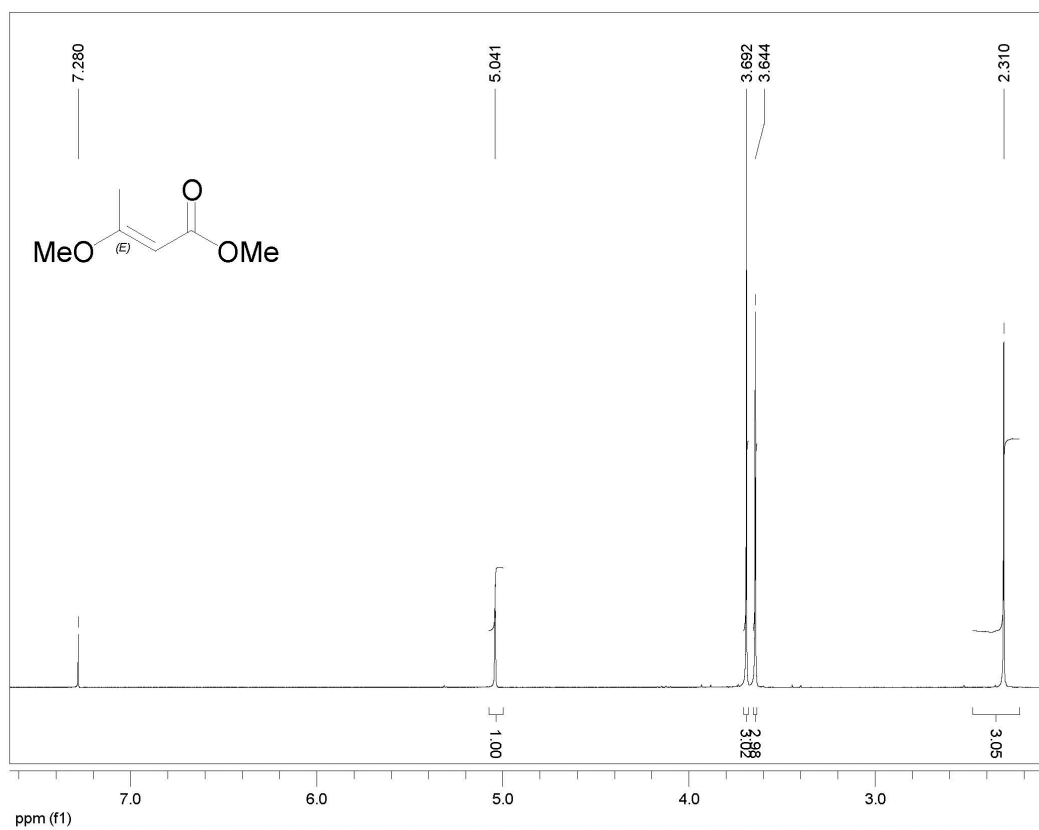


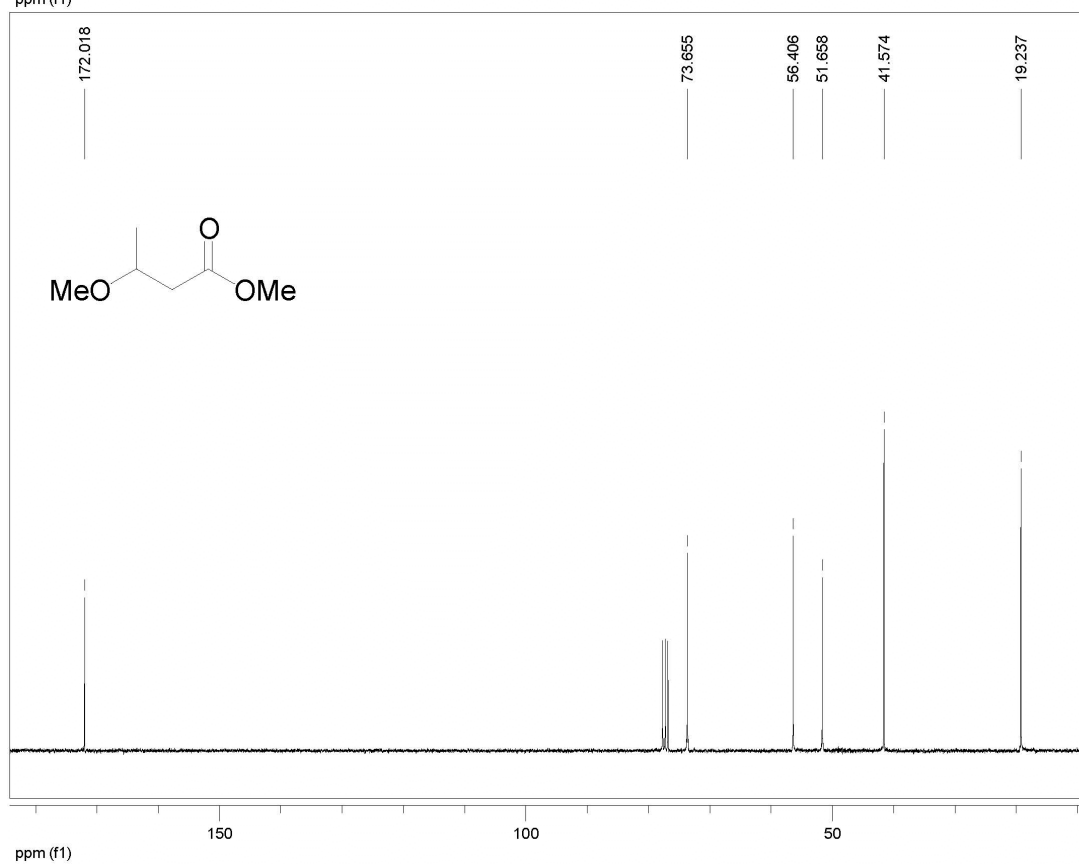
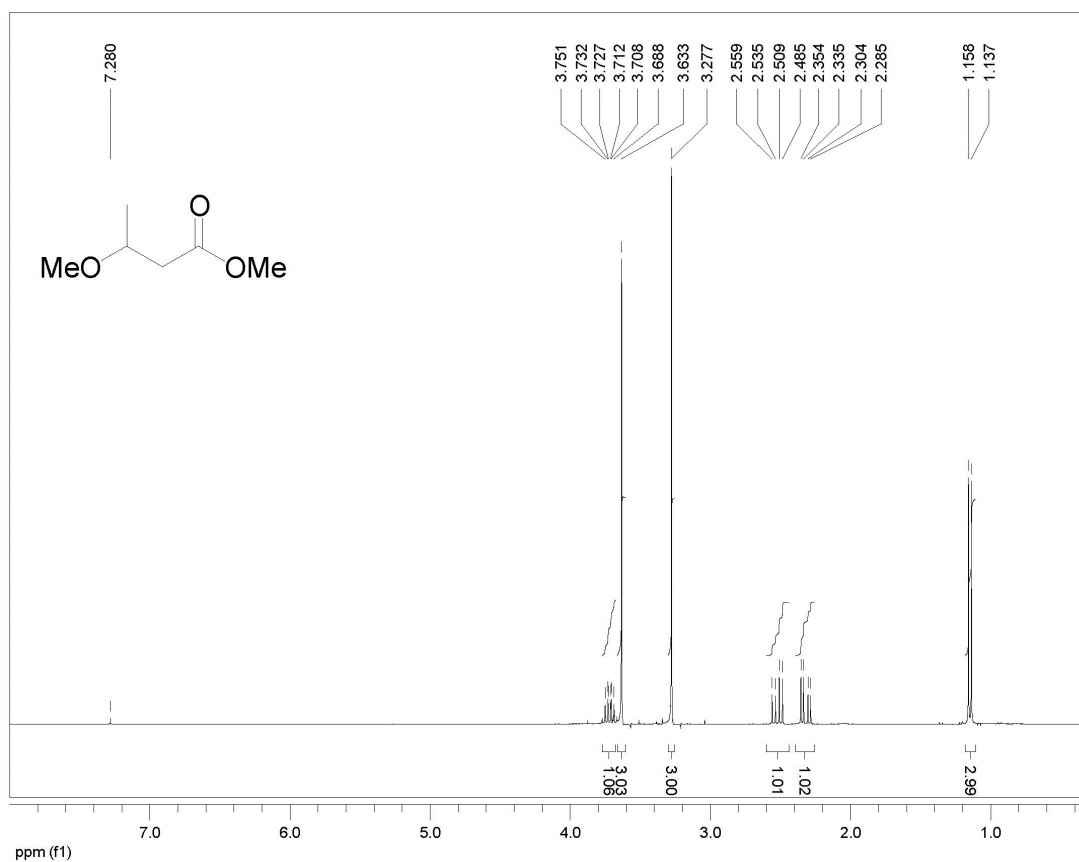
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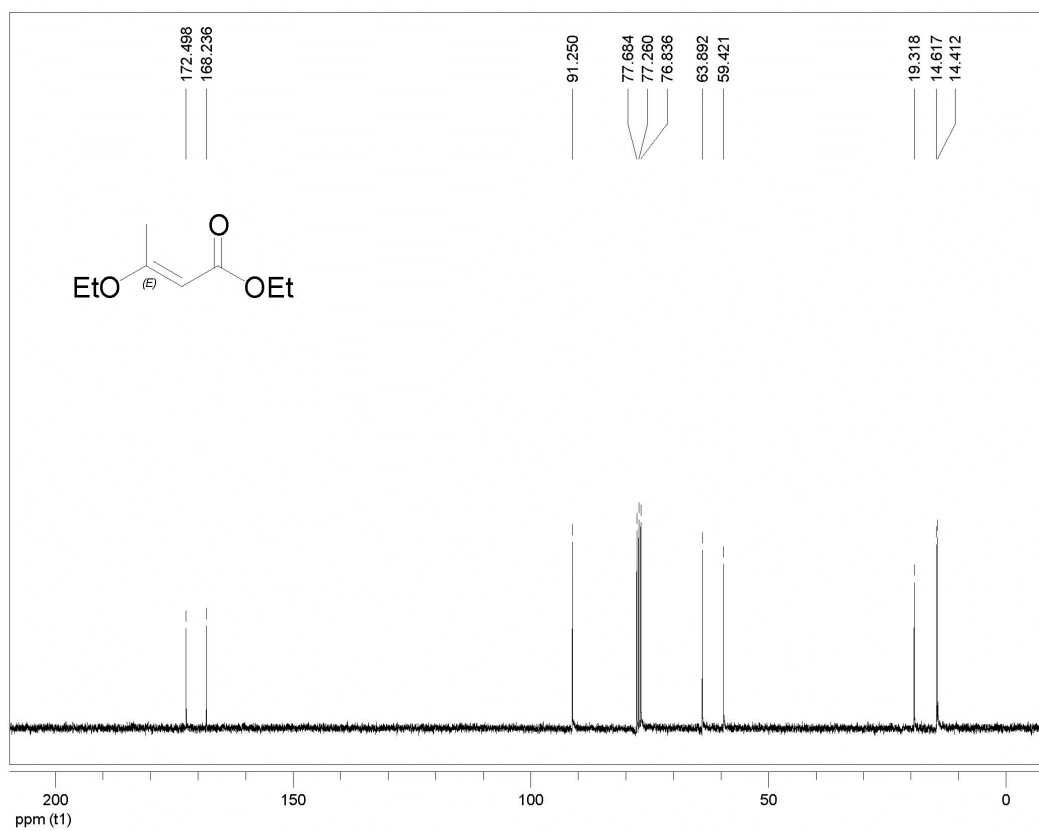
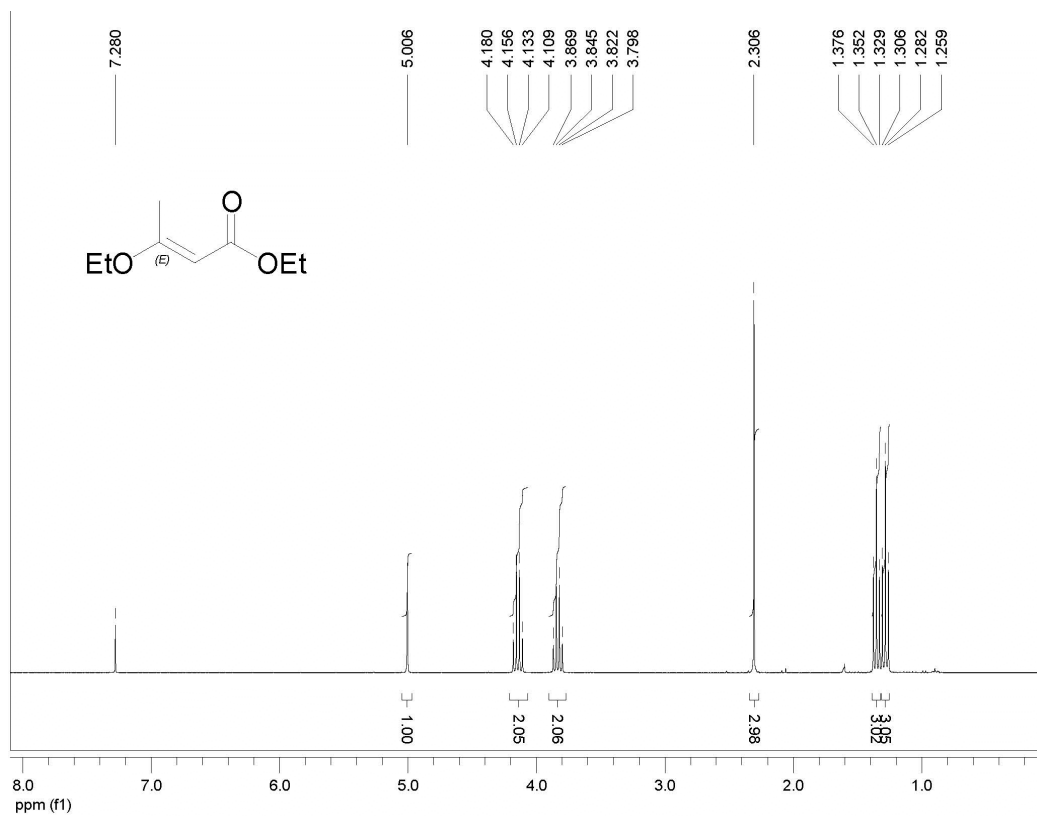
- 1) Armarego, W. L. F. and Perrin, D. D. Purification of Laboratory Chemicals; 4th Edition, Butterworth Heinemann, Oxford, **1996**.
- 2) Smissman, E. E.; Voldeng A. N., *J. Org. Chem.* **1964**, *11*, 3161.
- 3) Krebs, O.; Taylor, R. J. K., *Org. Lett.* **2005**, *6*, 1063.
- 4) Ireland, R.E.; Thaisrivongs, S.; Vanier, I.N.; Wilcox, C. S., *J. Org. Chem.* **1980**, *1*, 48.
- 5) Stereochemistry assumed to be (Z)-olefin based on comparing the ¹H NMR with other substrates.
- 6) Need adding 1 equivalent anhydrous K₂CO₃.
- 7) Staerk D. U., Shitangkoon A., Vigh G., *J. Chromatogr. A.* **1995**, *702*, 251.
- 8) Get the true sample from Aldrich Company.
- 9) Evans D. A.; Ratz A. M.; Huff B. E.; Sheppard G. S., *Tetrahedron Lett.* **1994**, *39*, 7171.
- 10) Genet J. P.; Ratovelomanana-Vidal V.; Pfister X.; Guerriero P.; Lenoir J.Y., *Tetrahedron Lett.* **1995**, *27*, 4801.

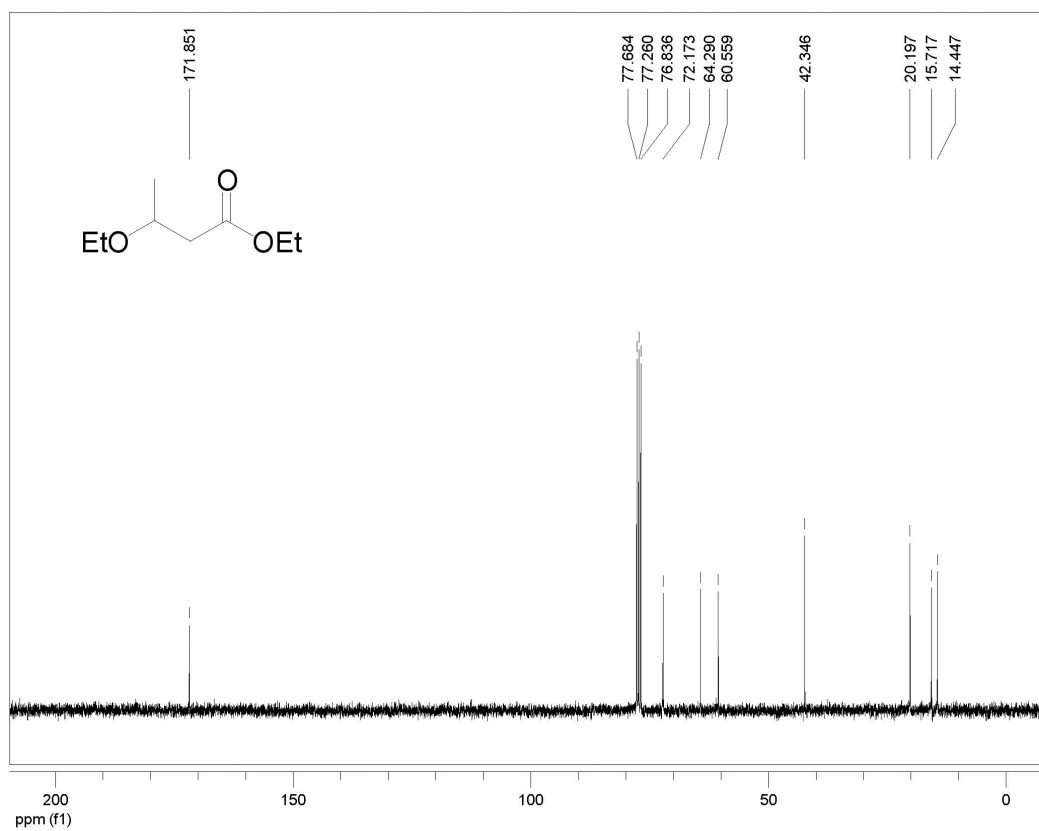
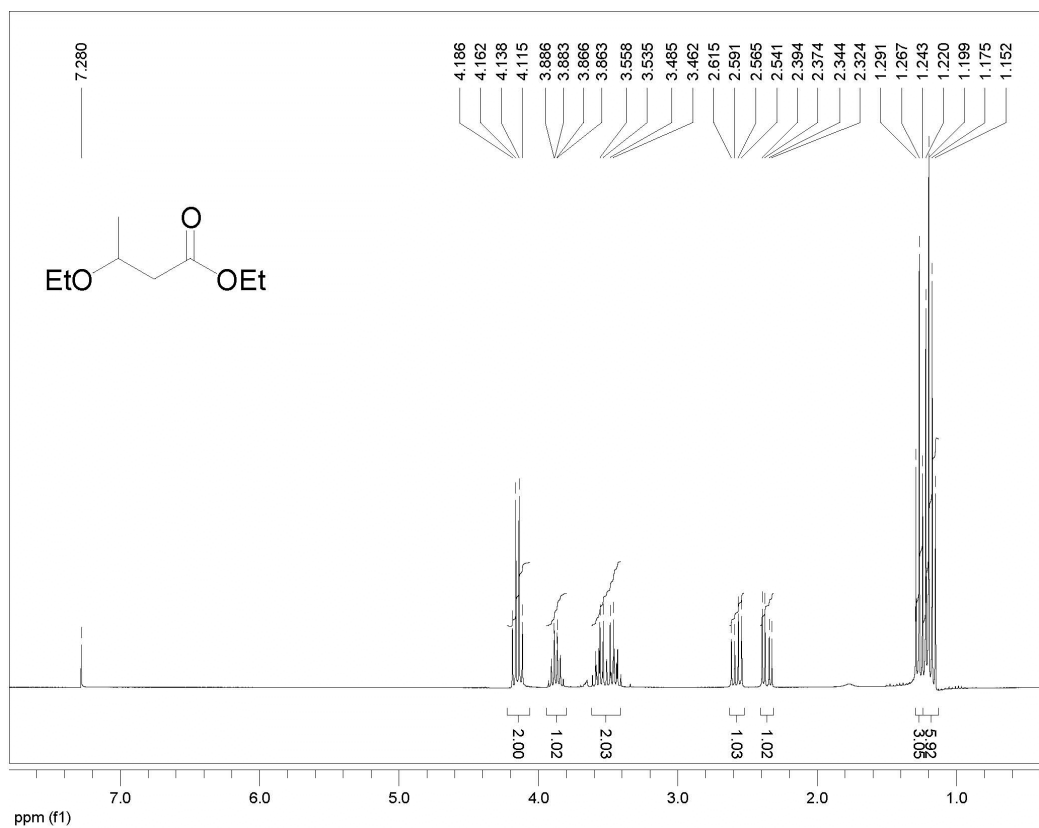


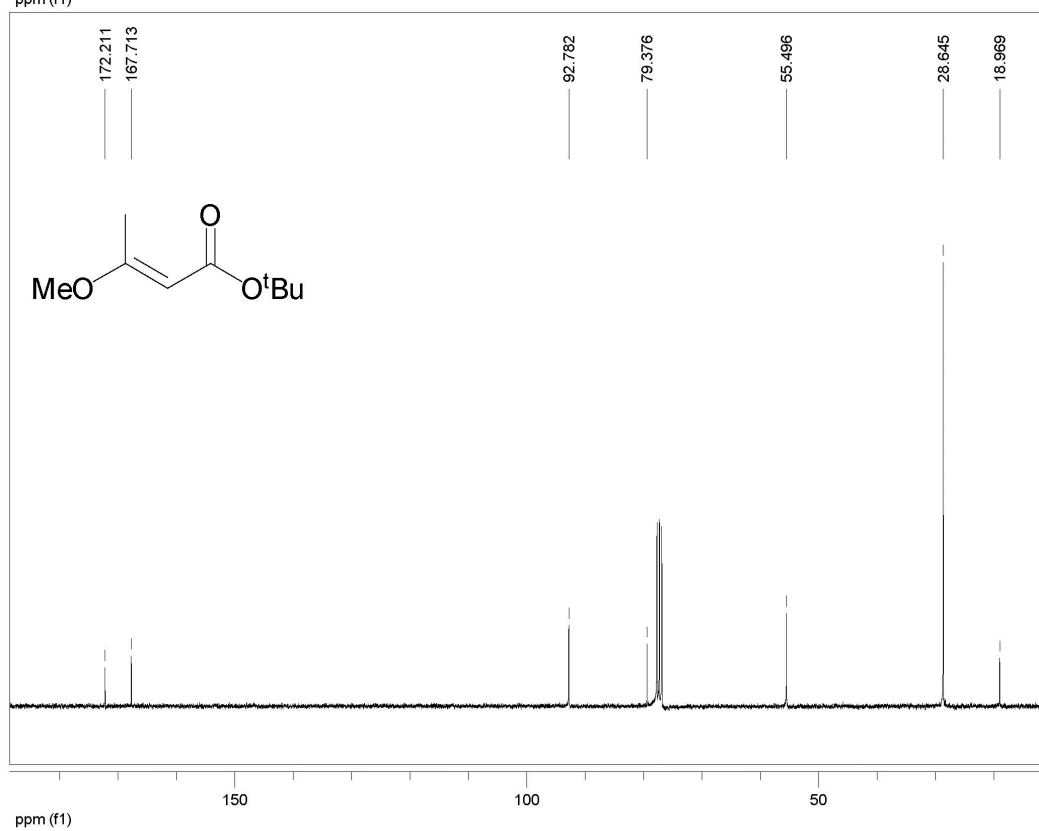
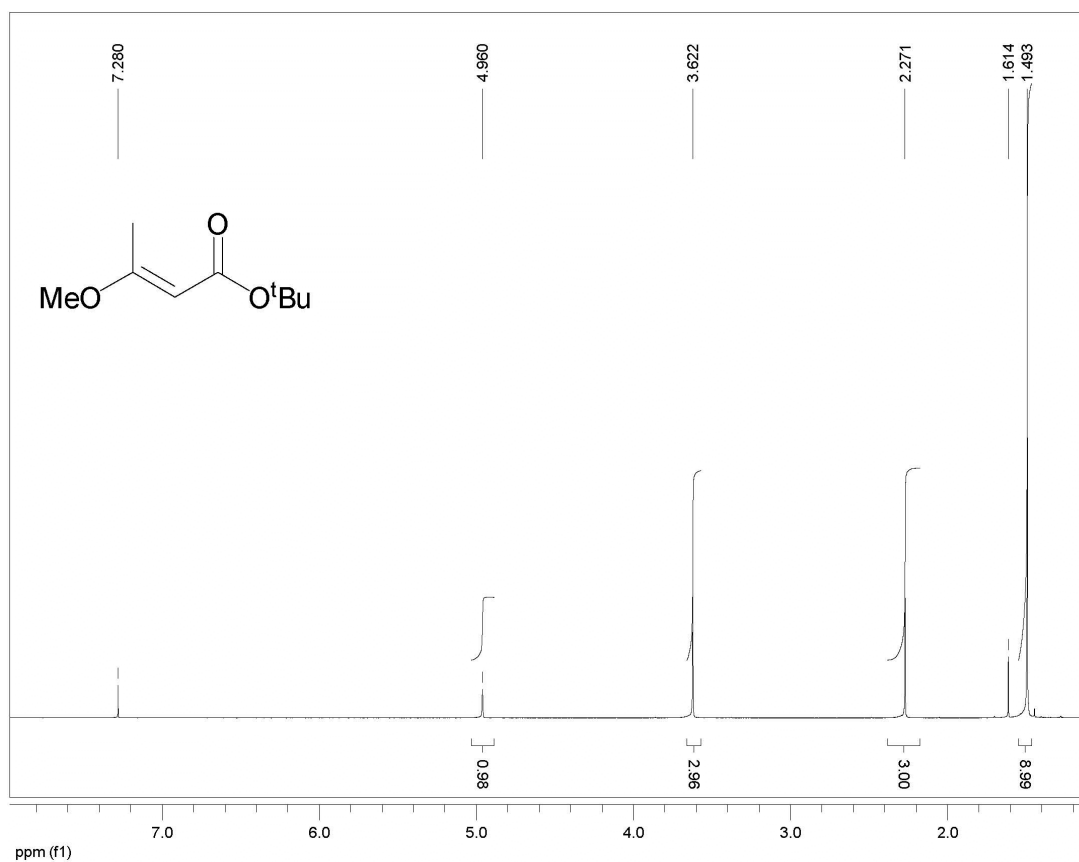


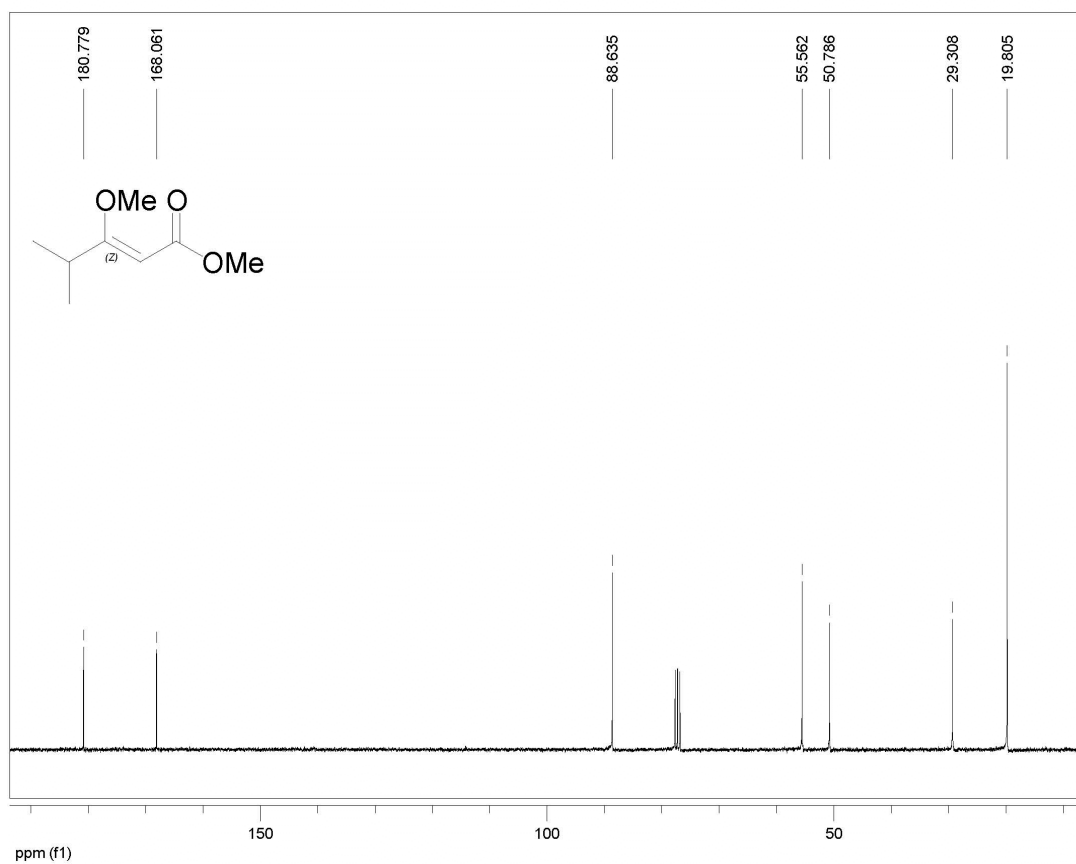
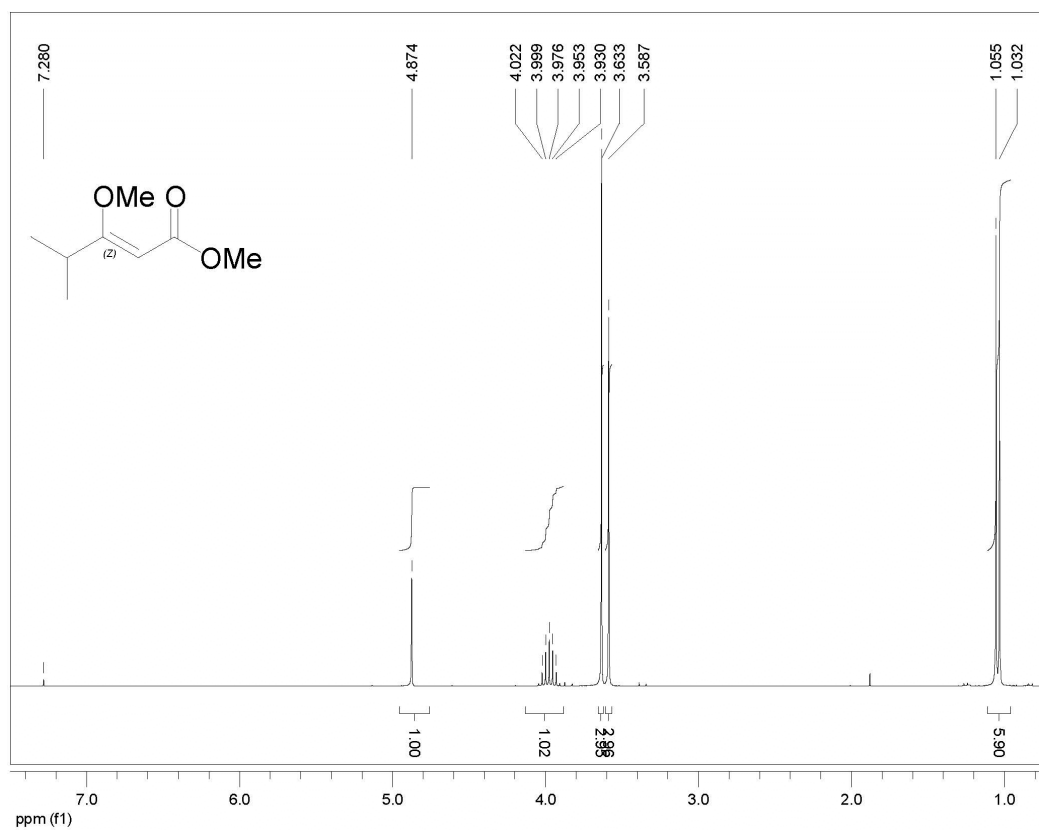


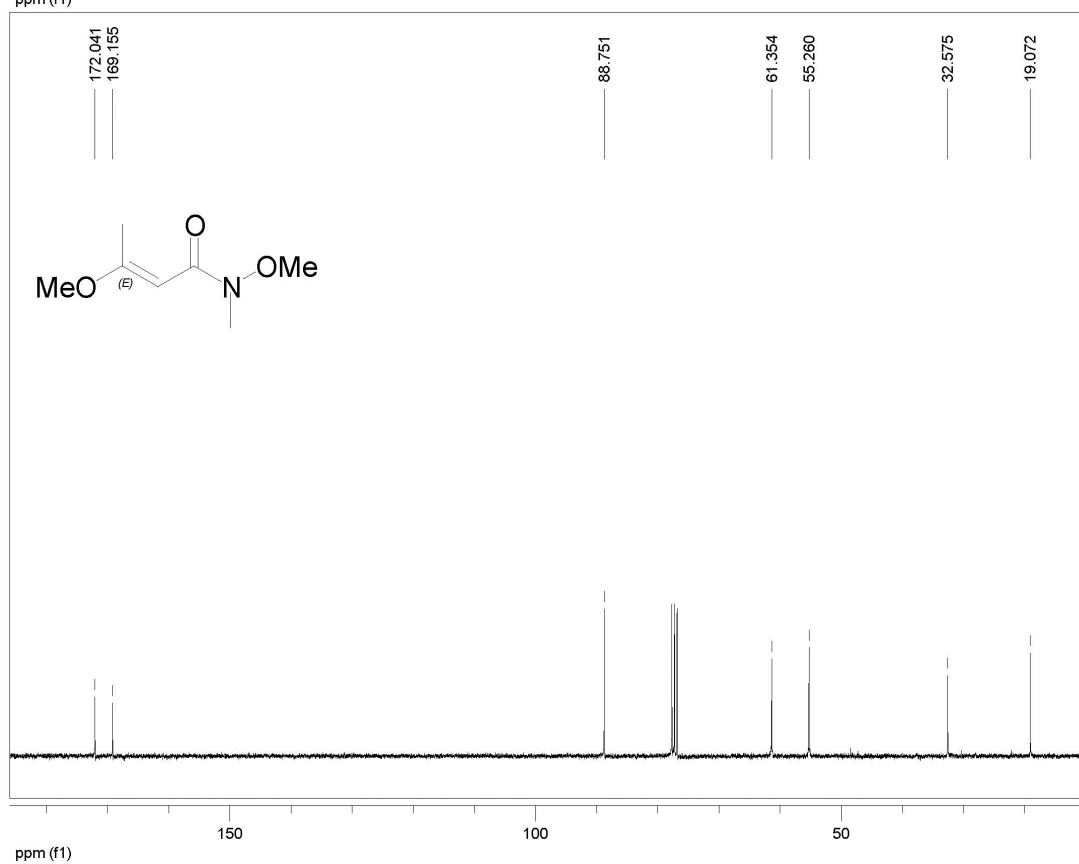
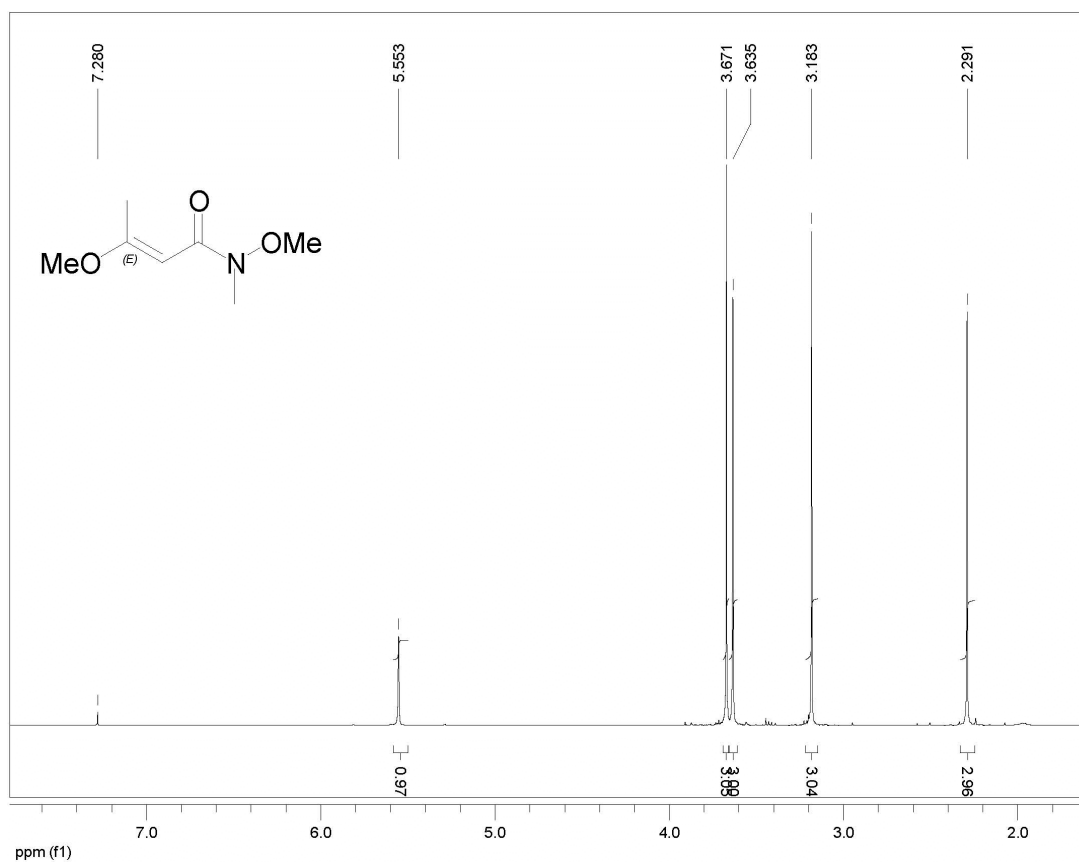


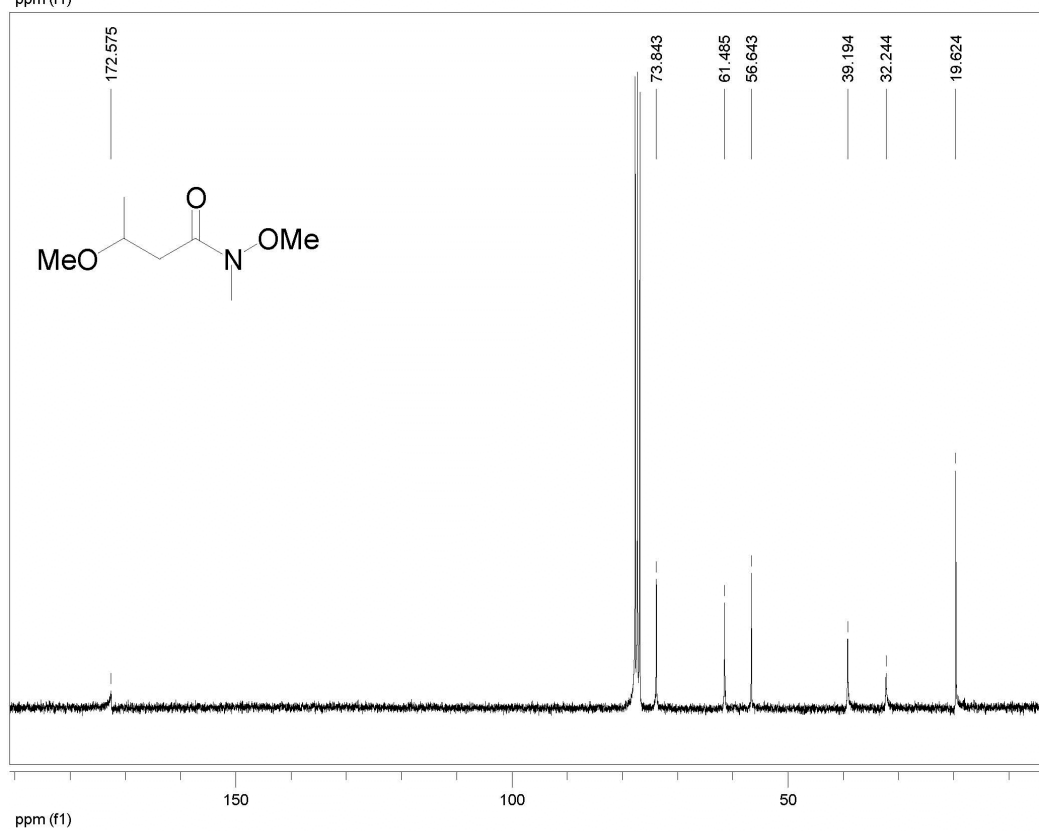
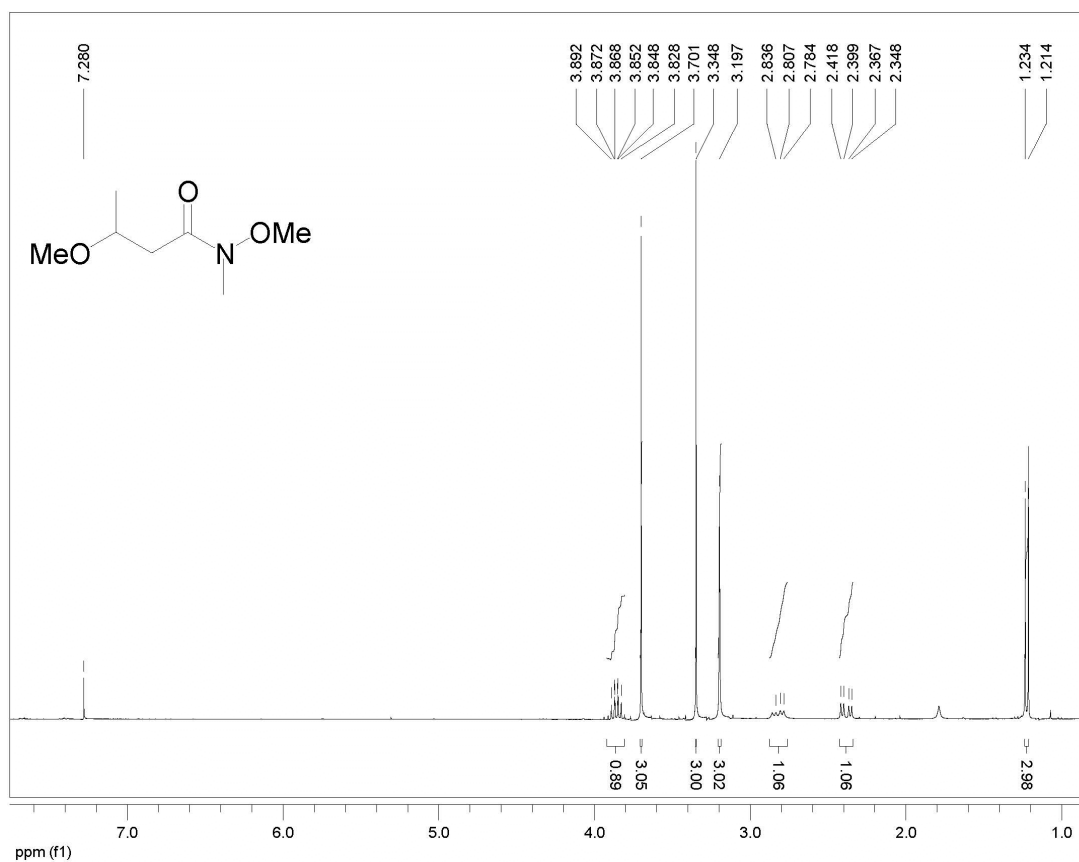


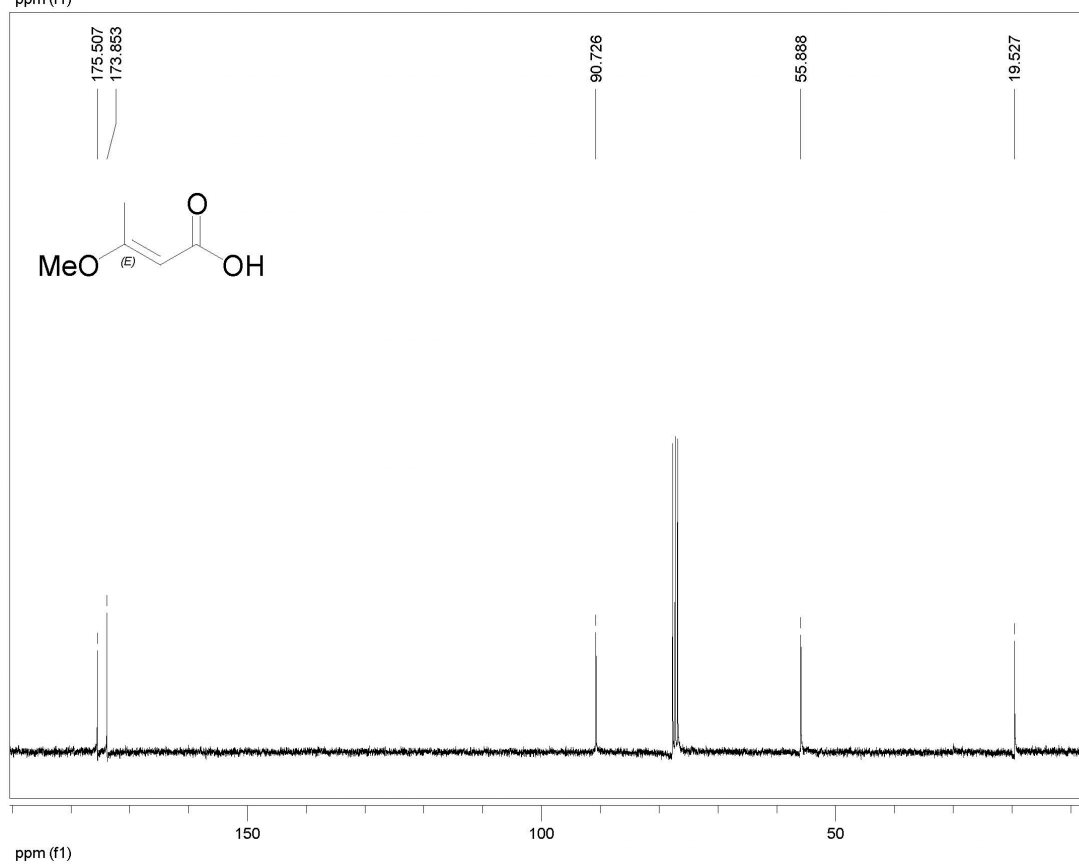
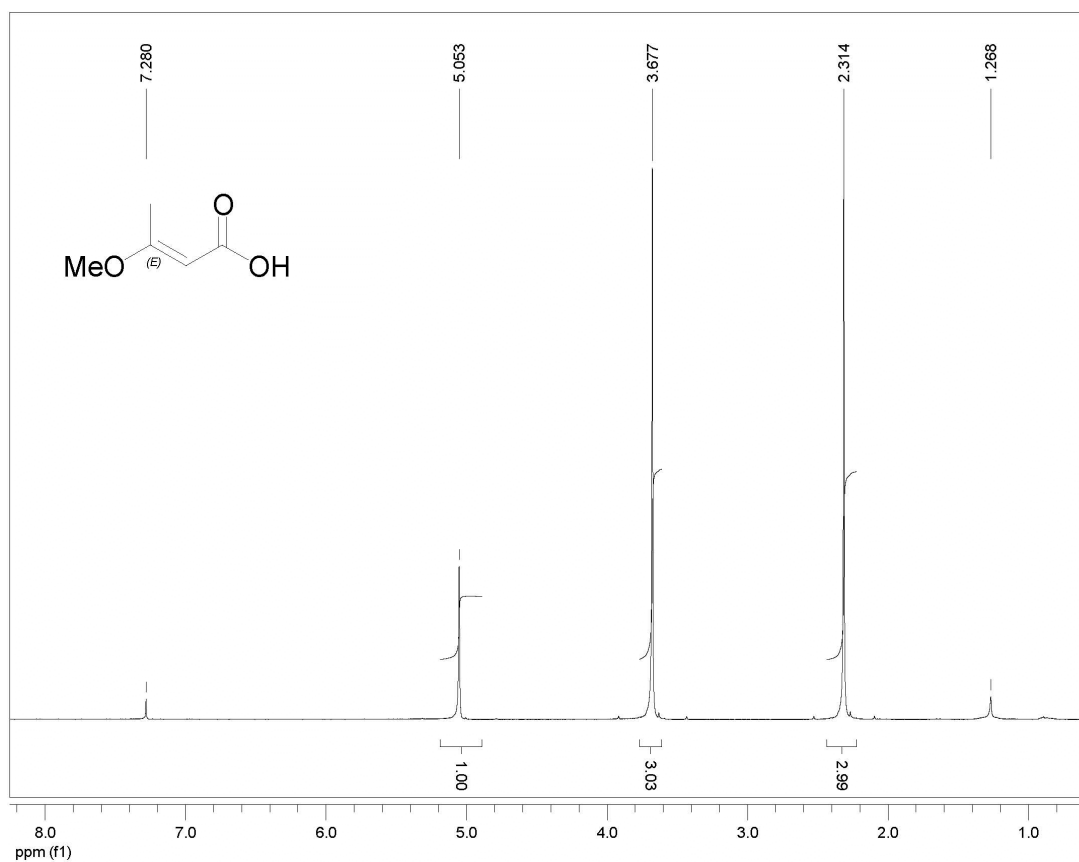


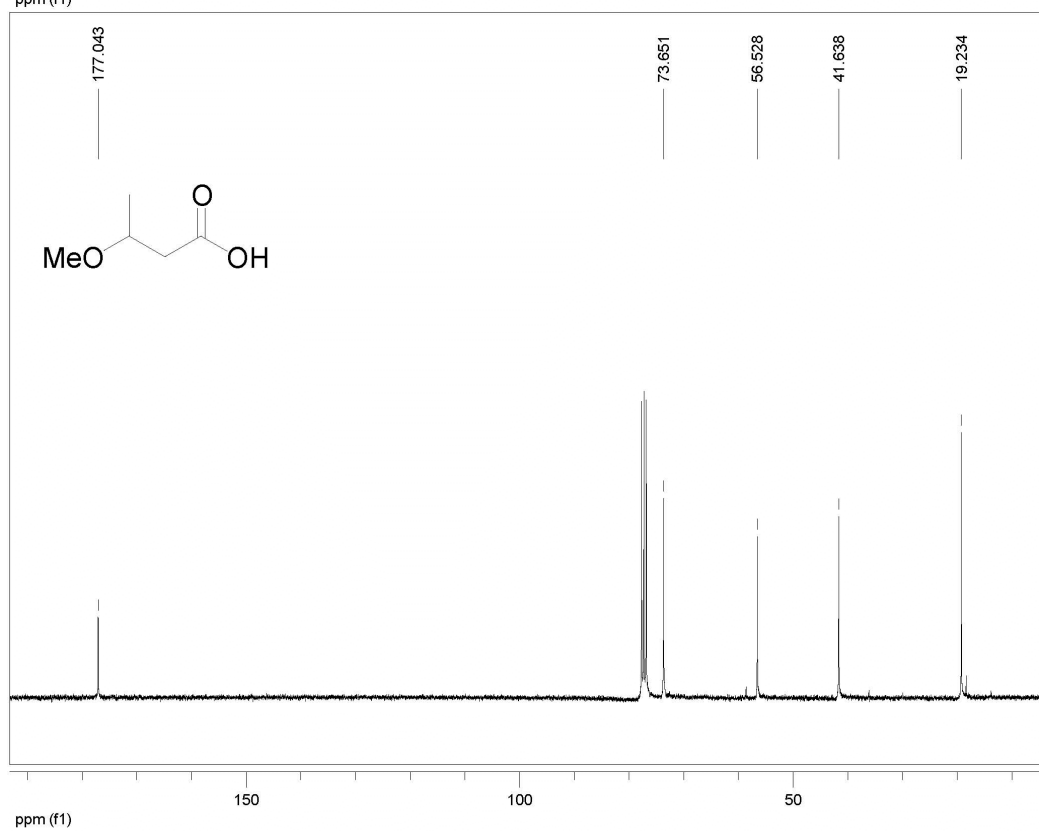
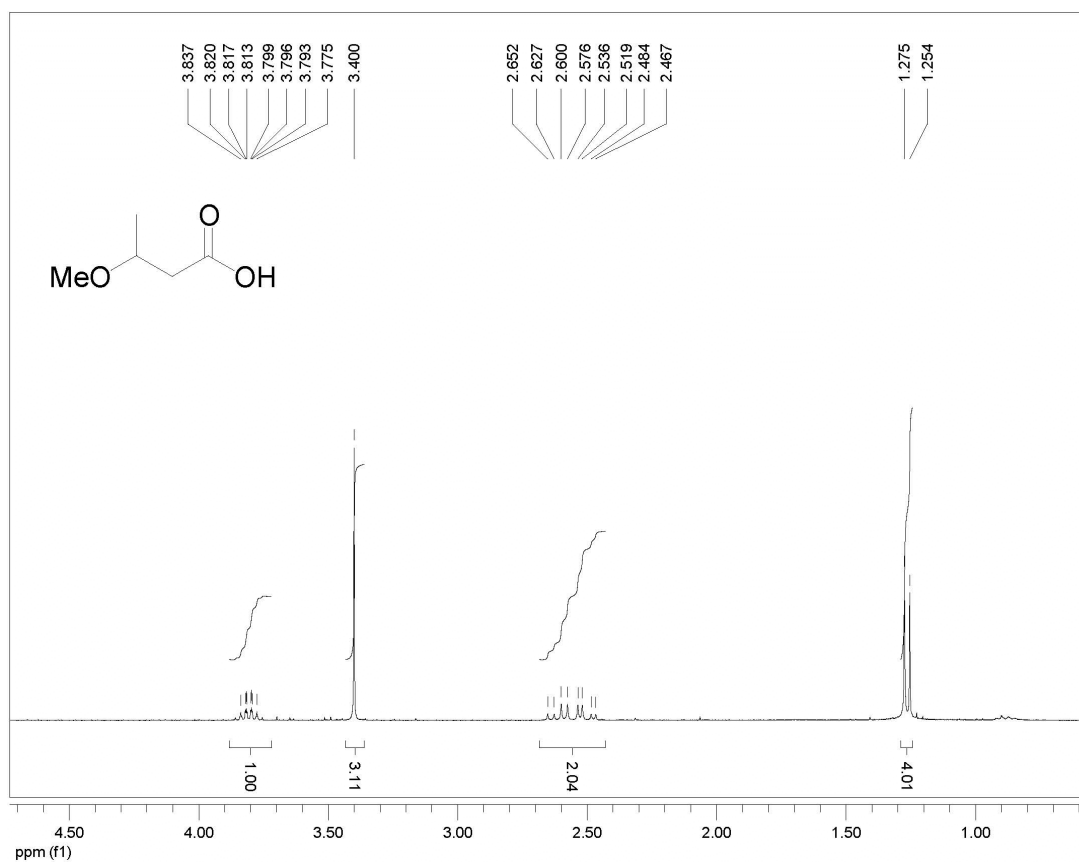


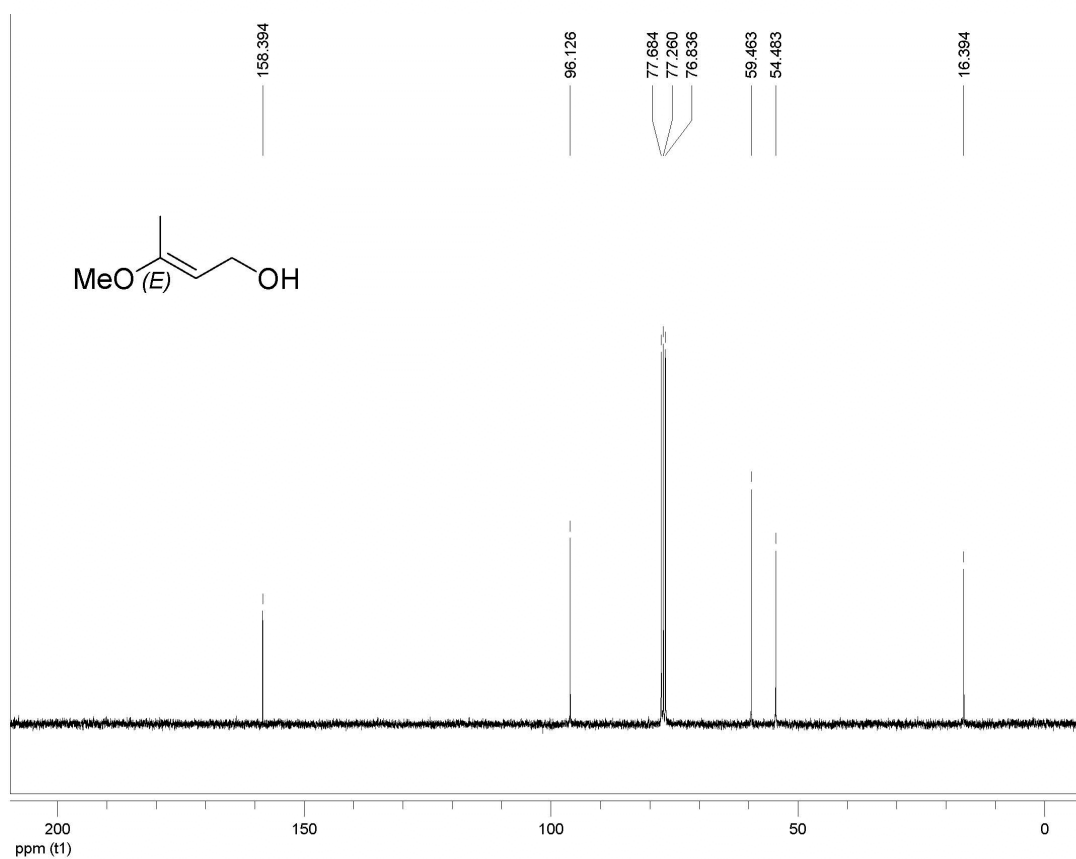
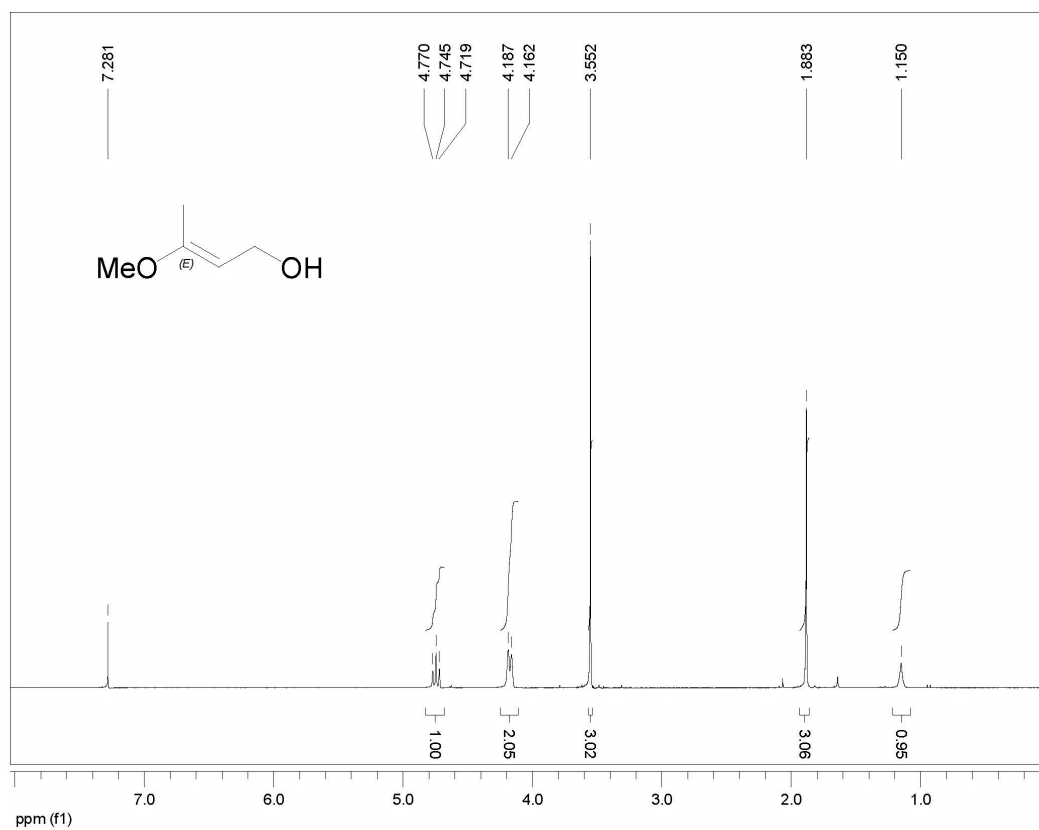


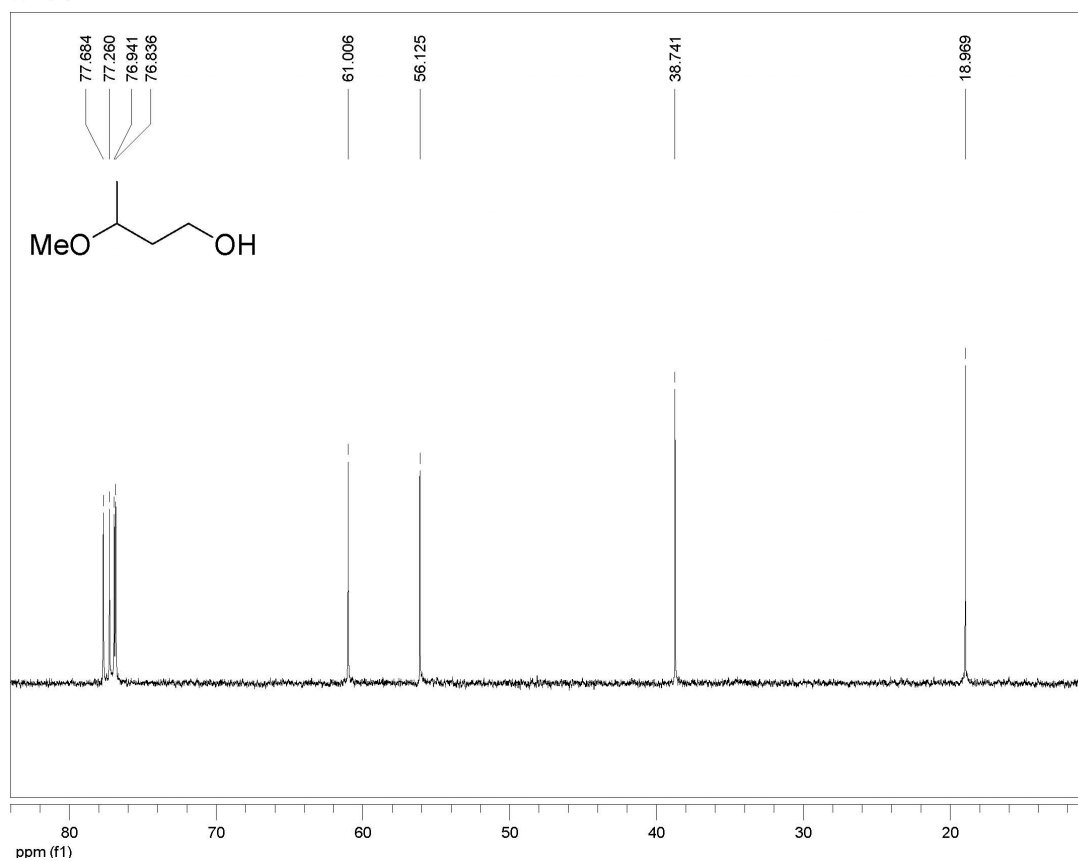
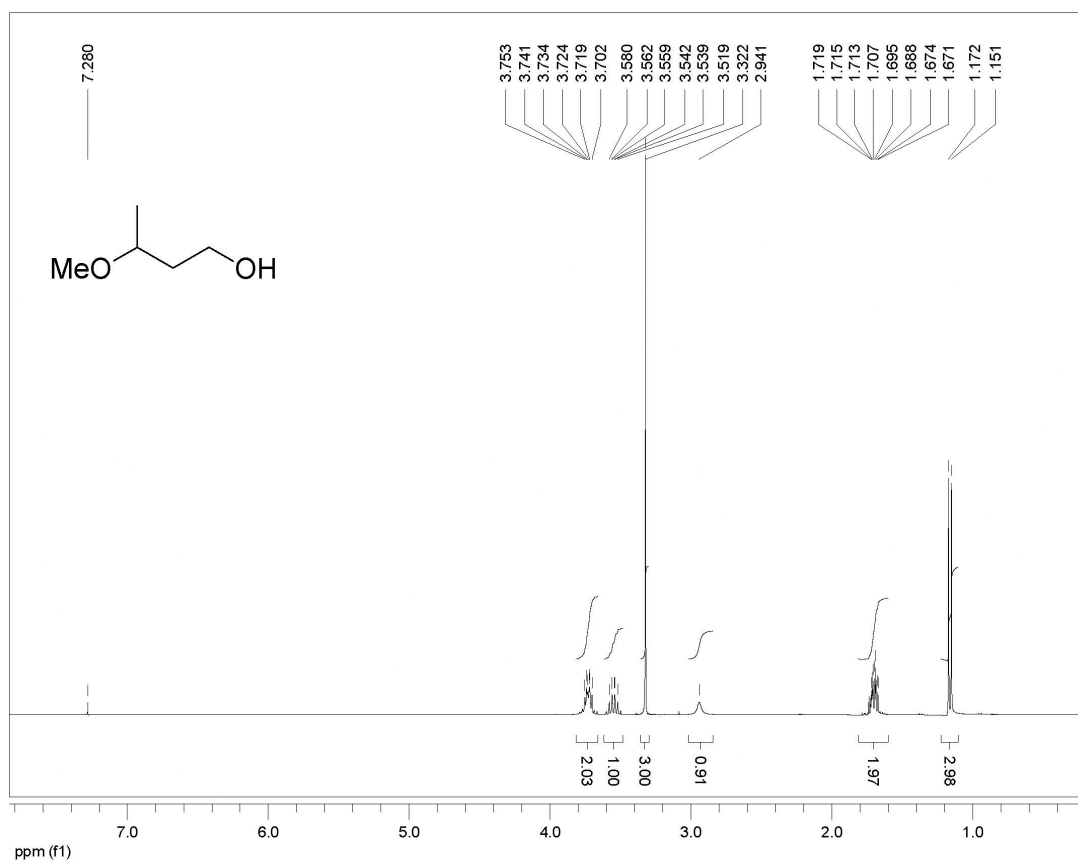


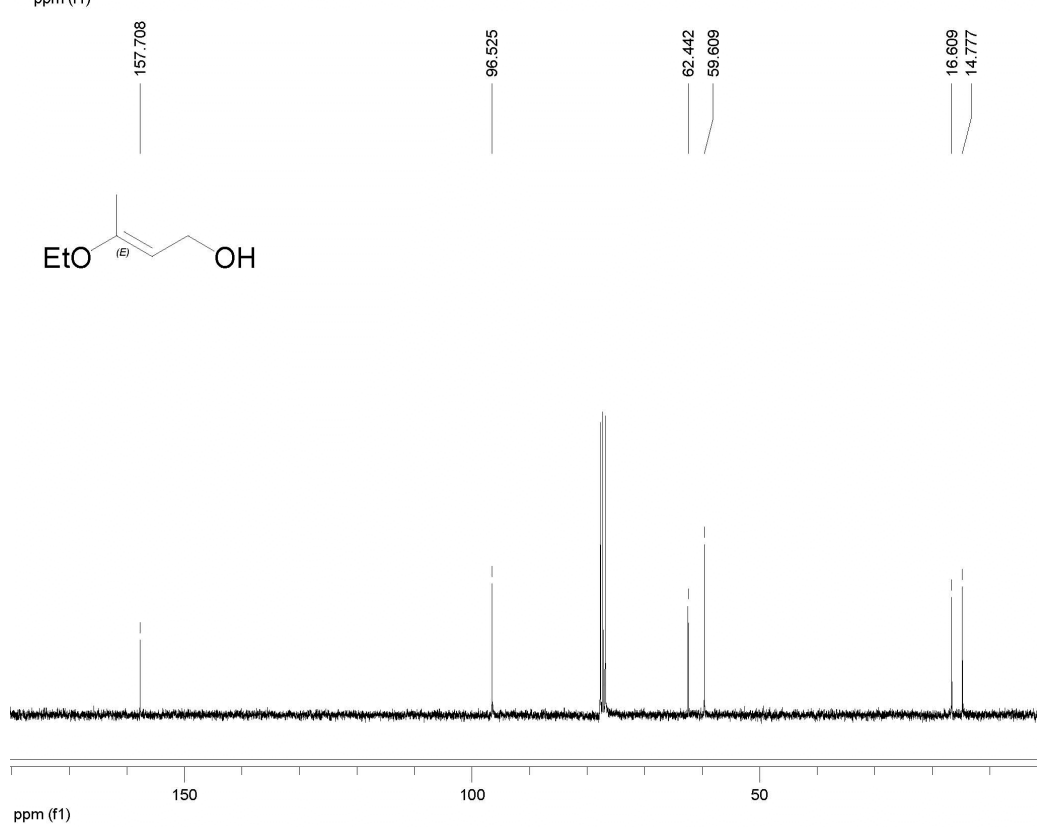
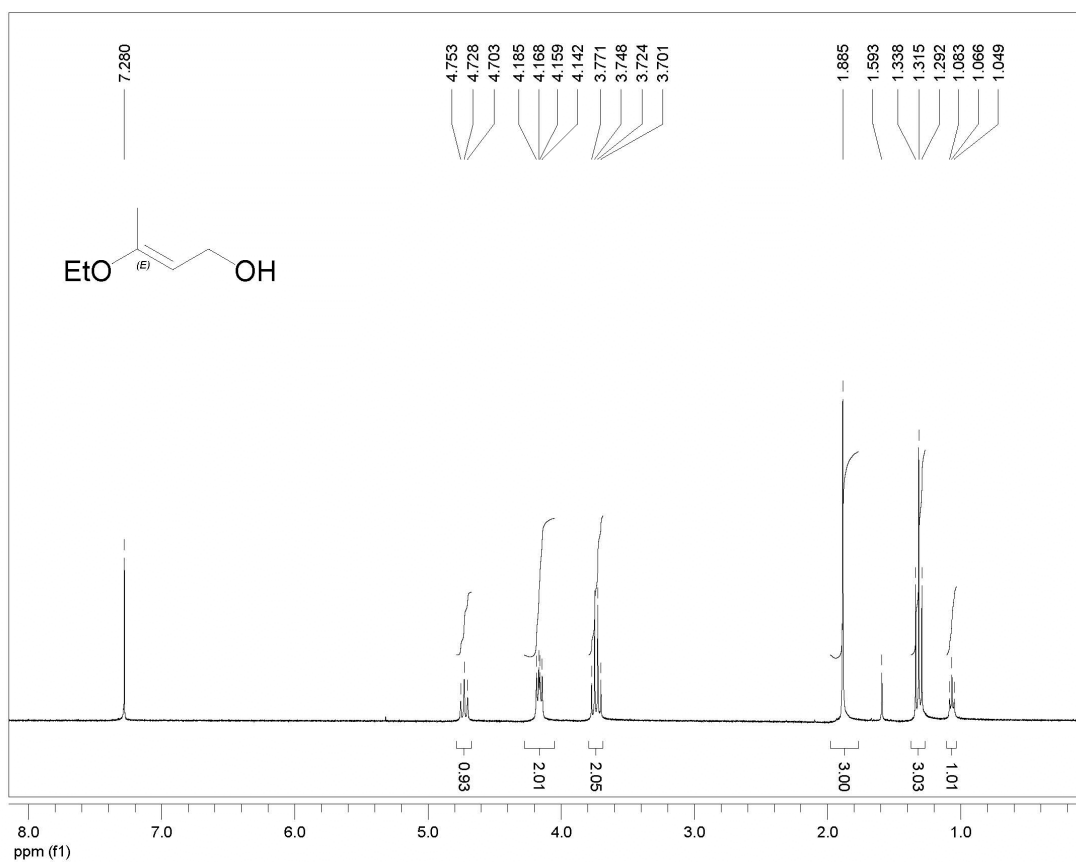


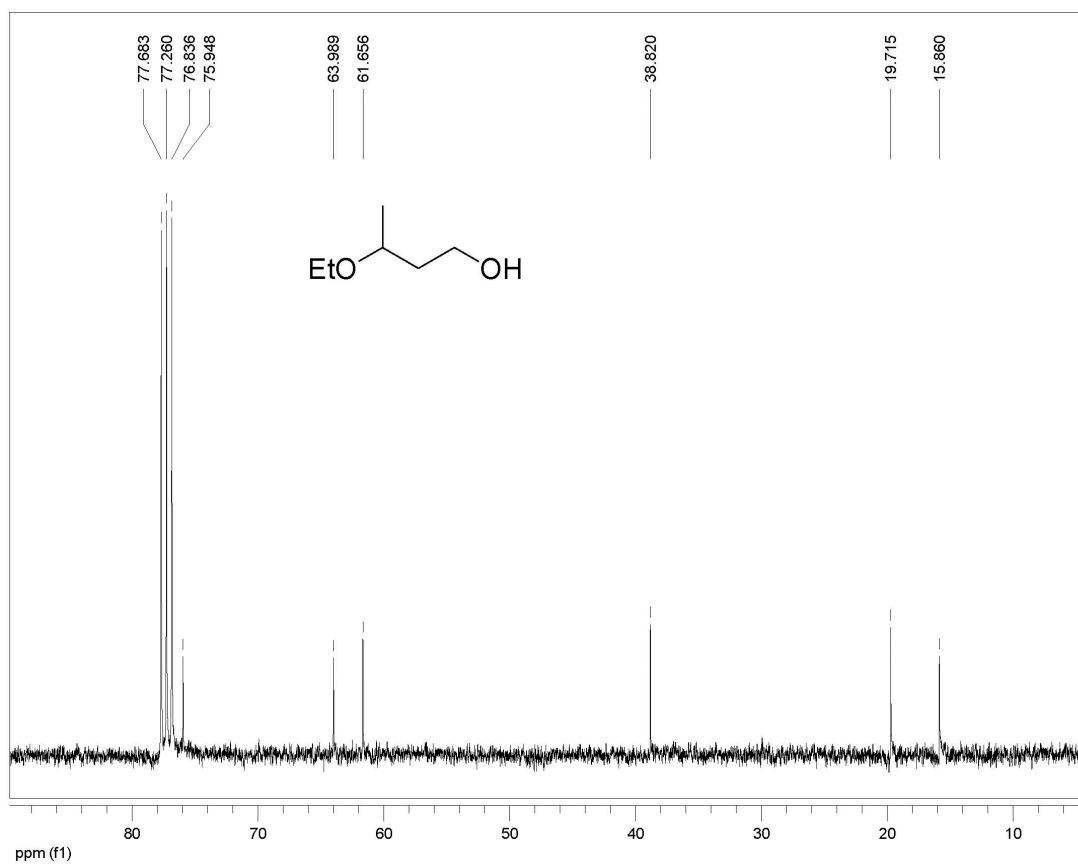
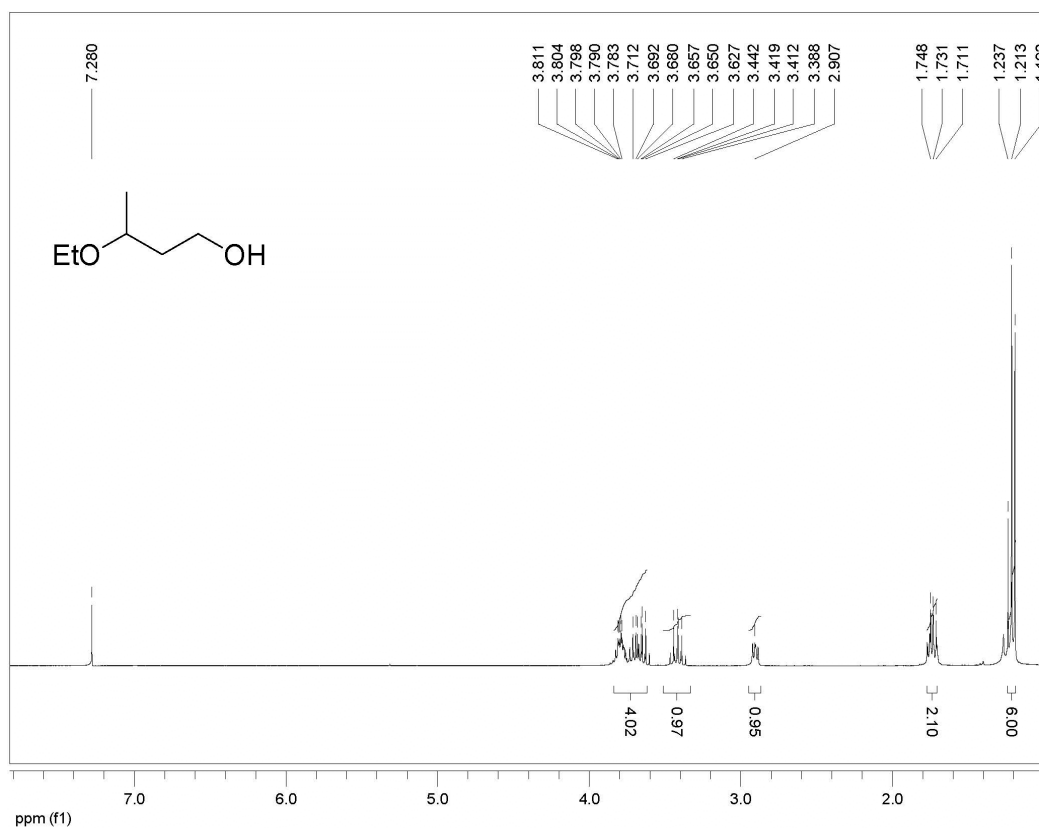


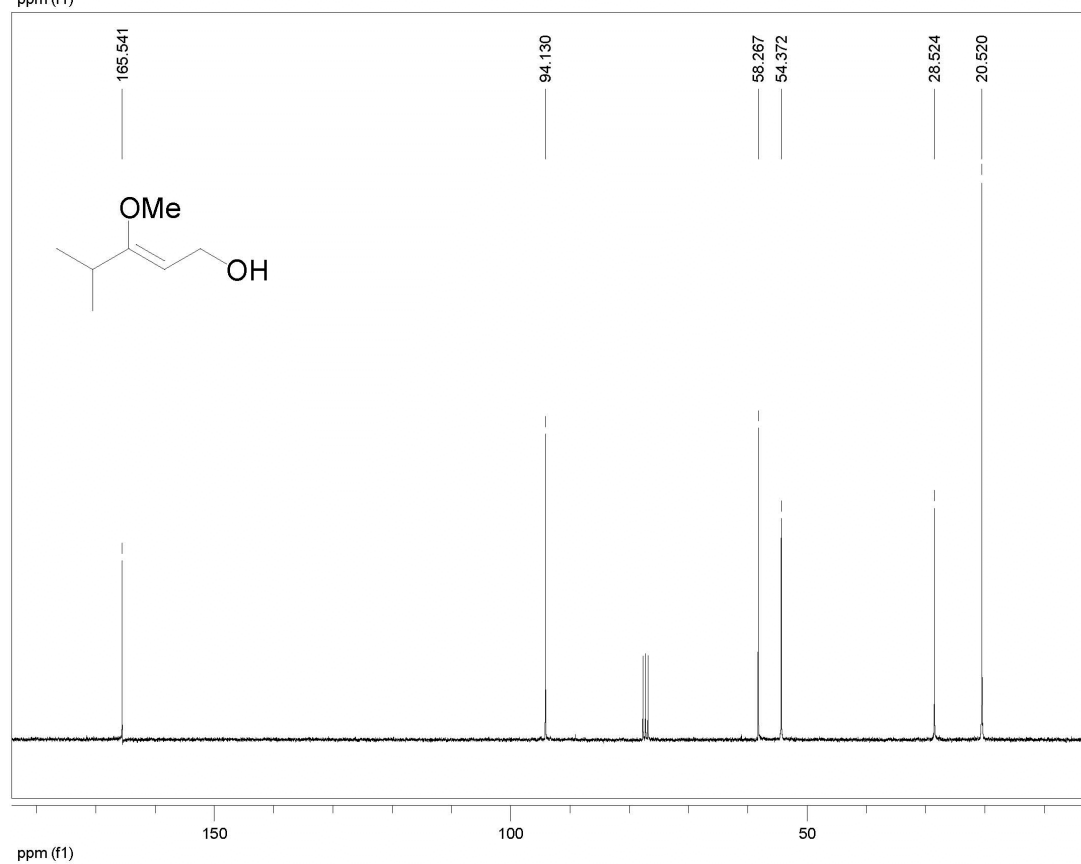
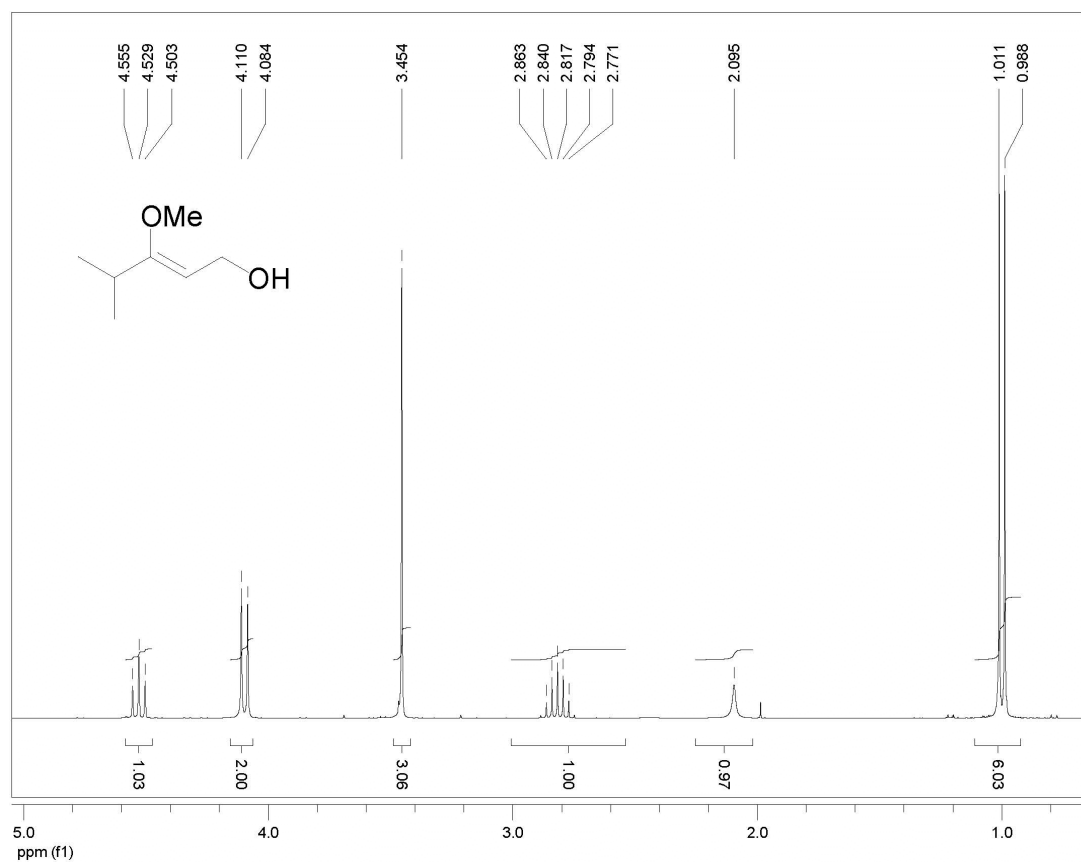


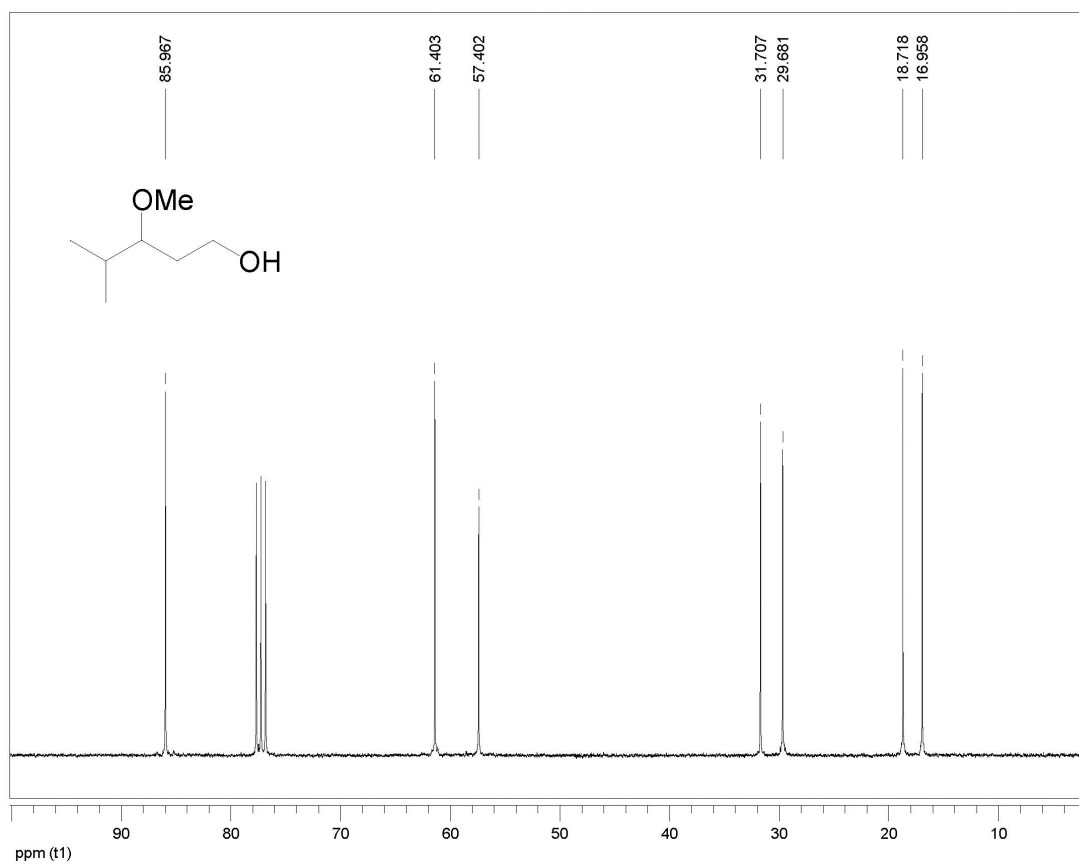
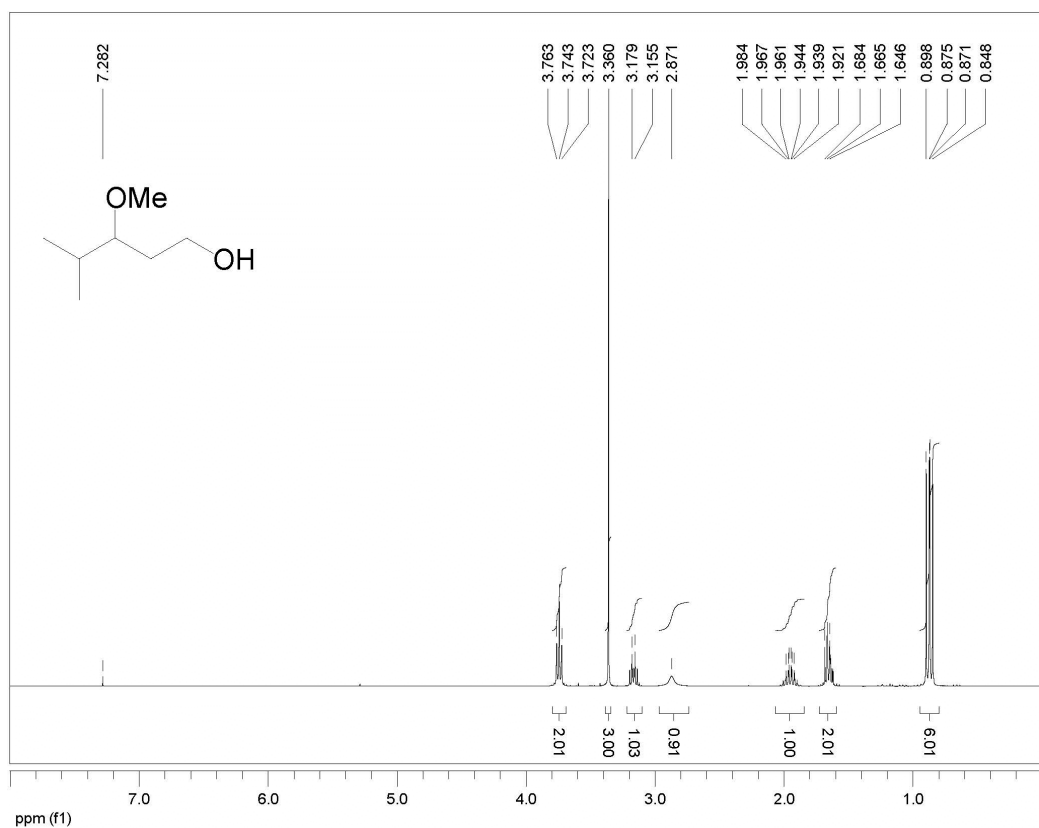


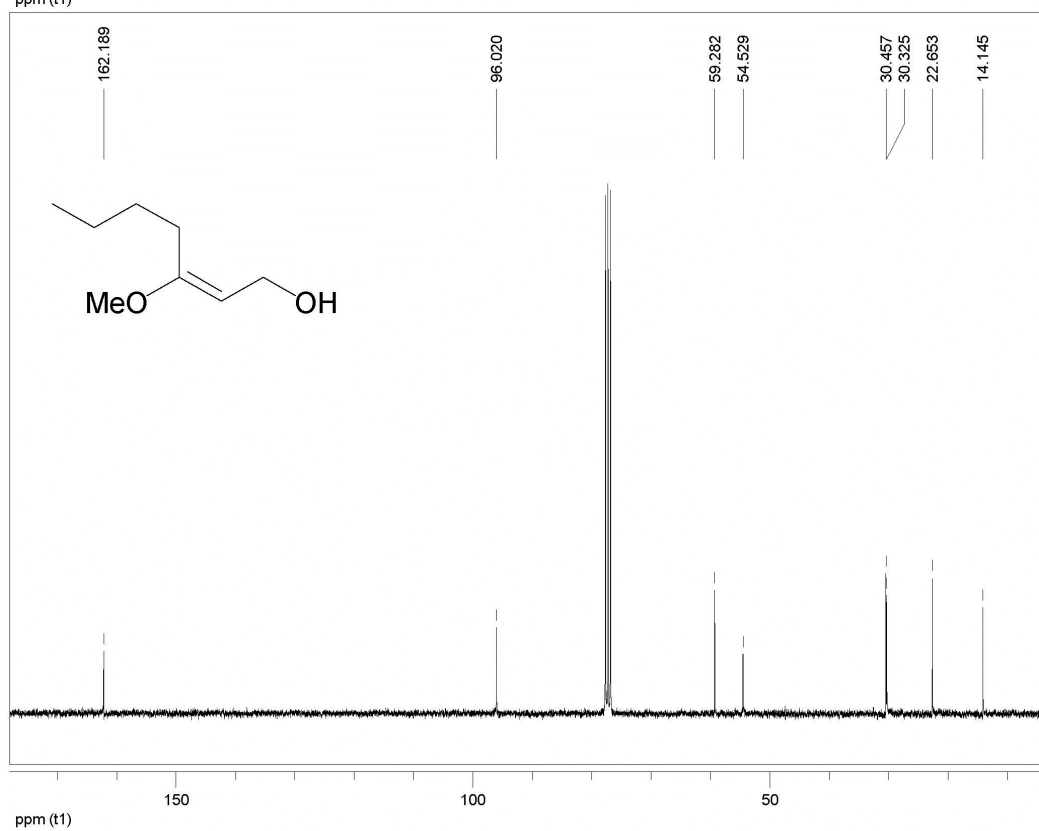
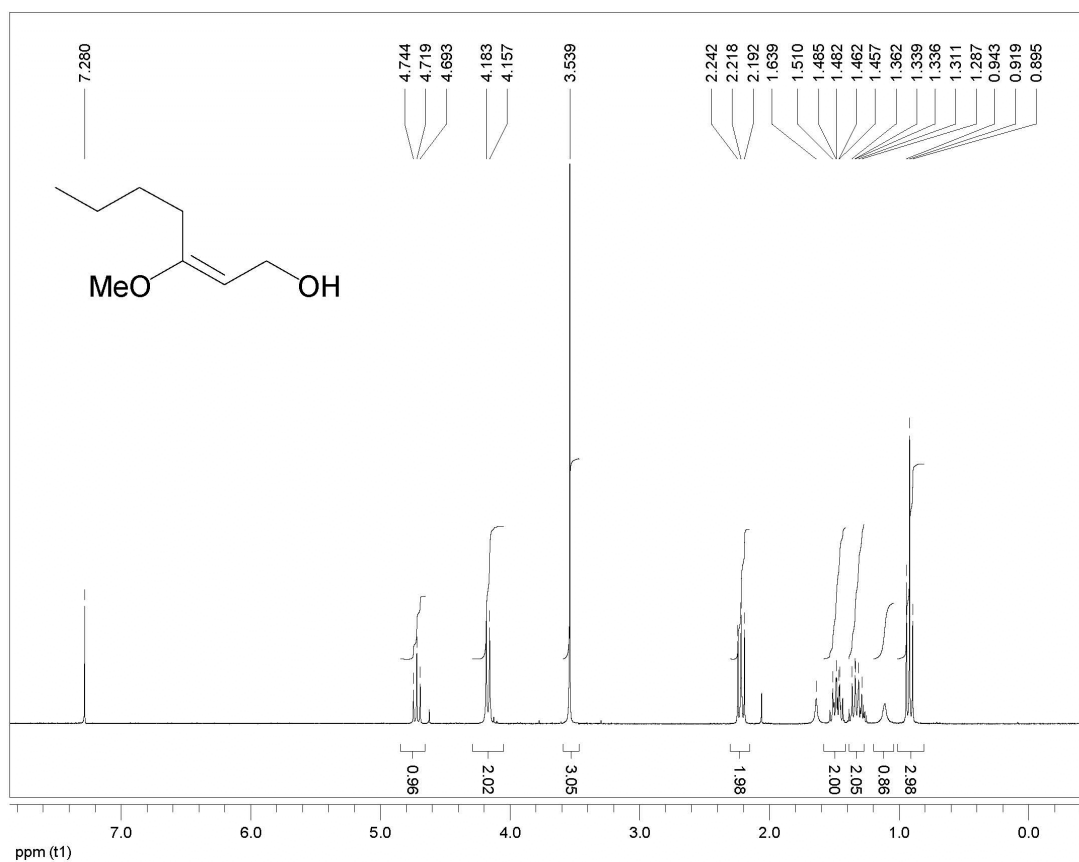


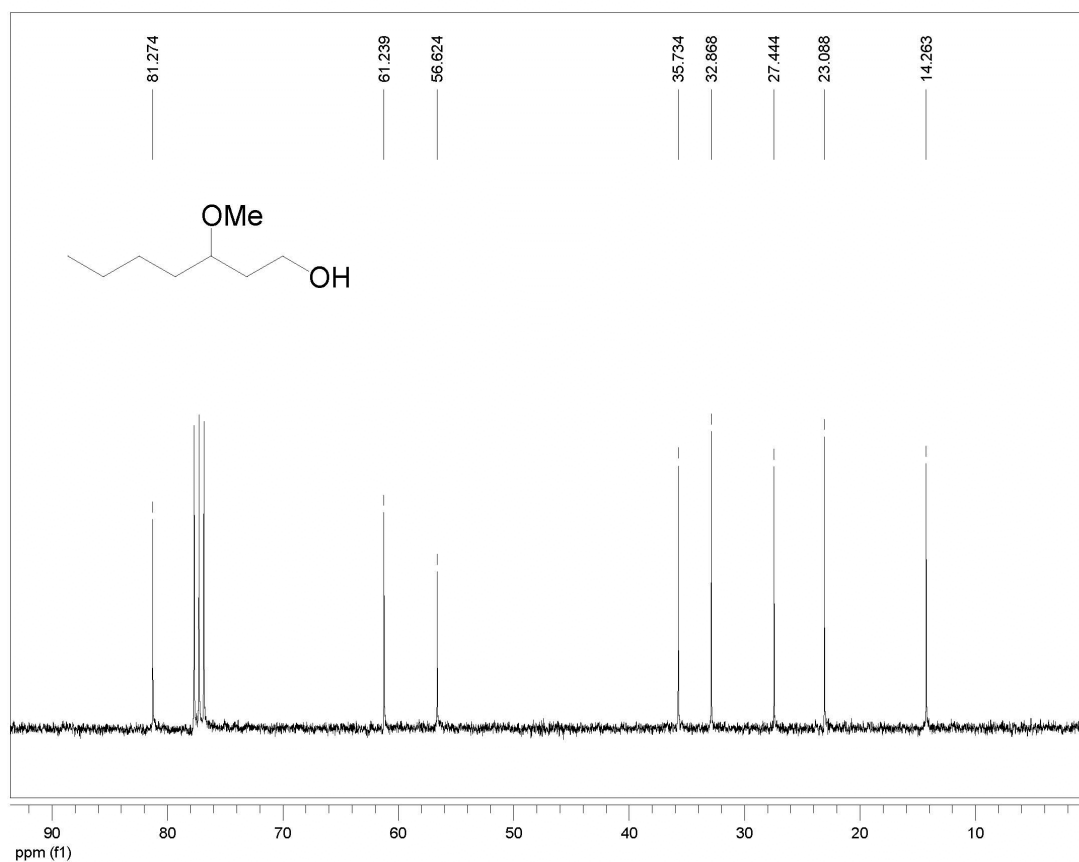
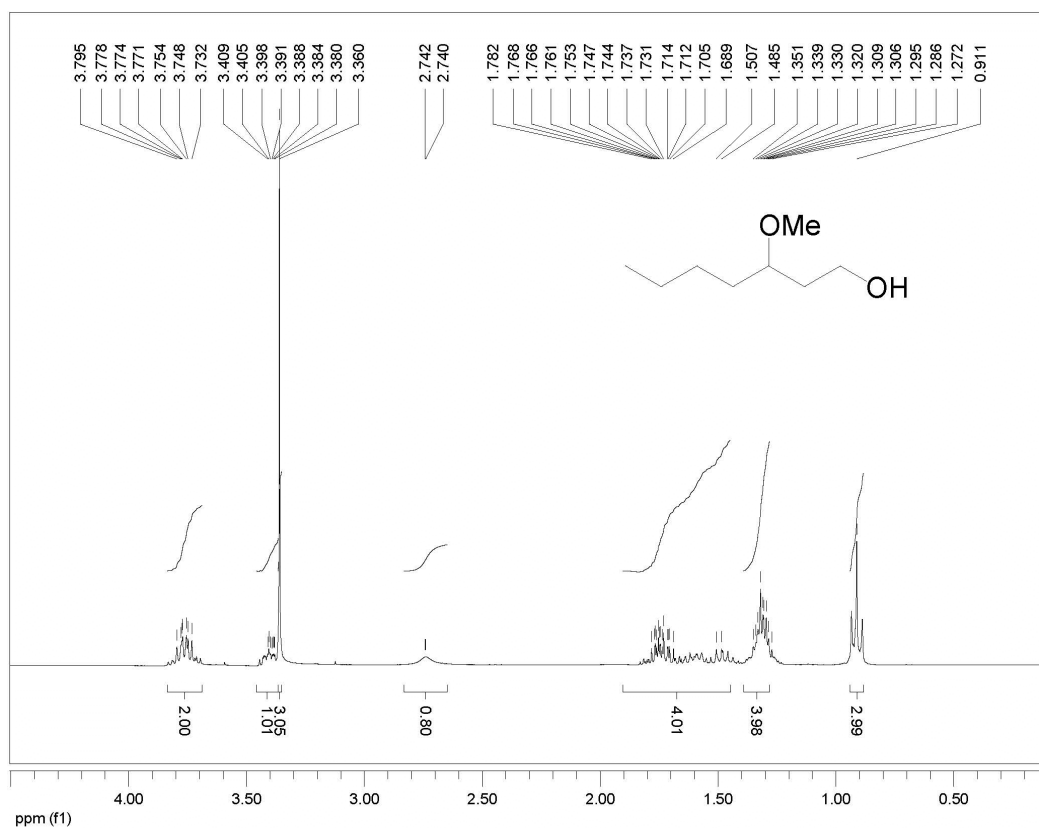


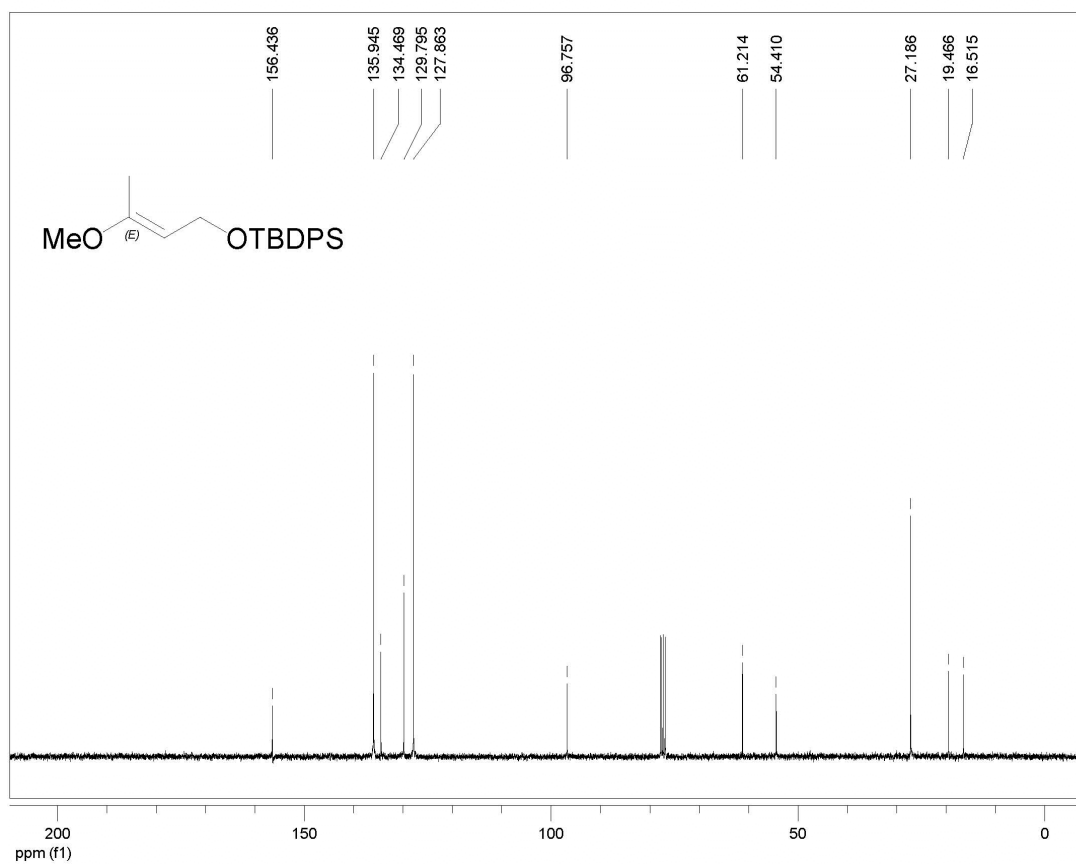
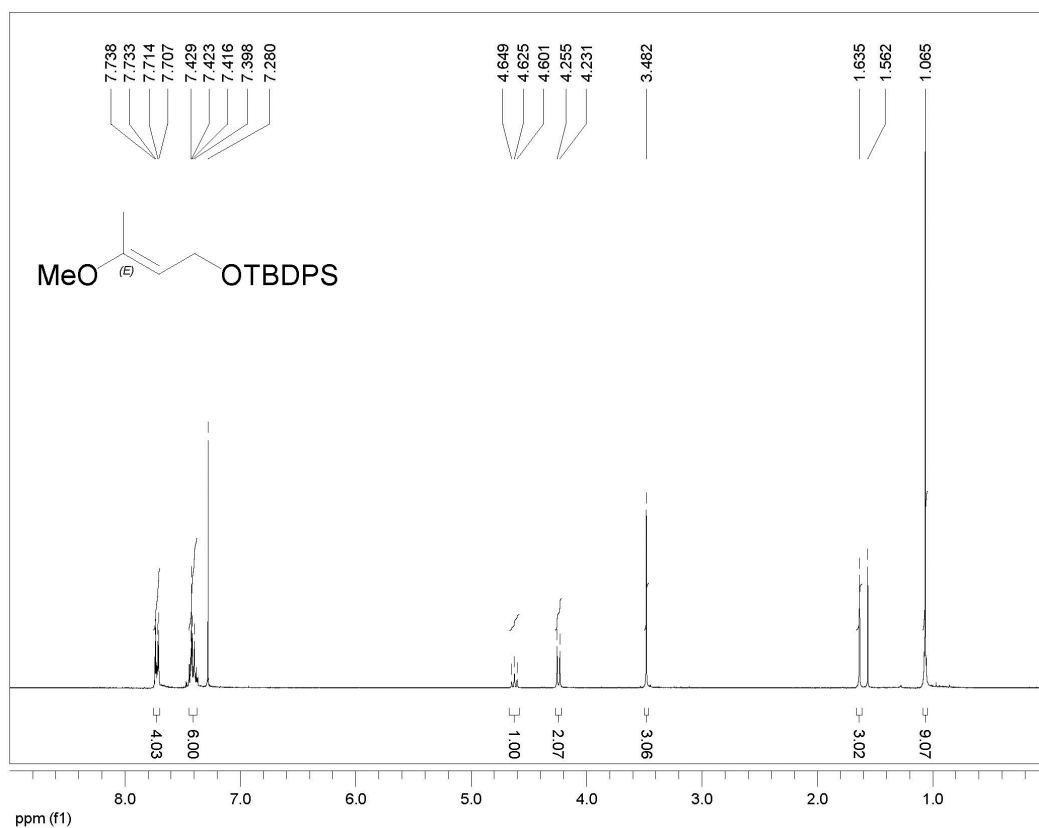


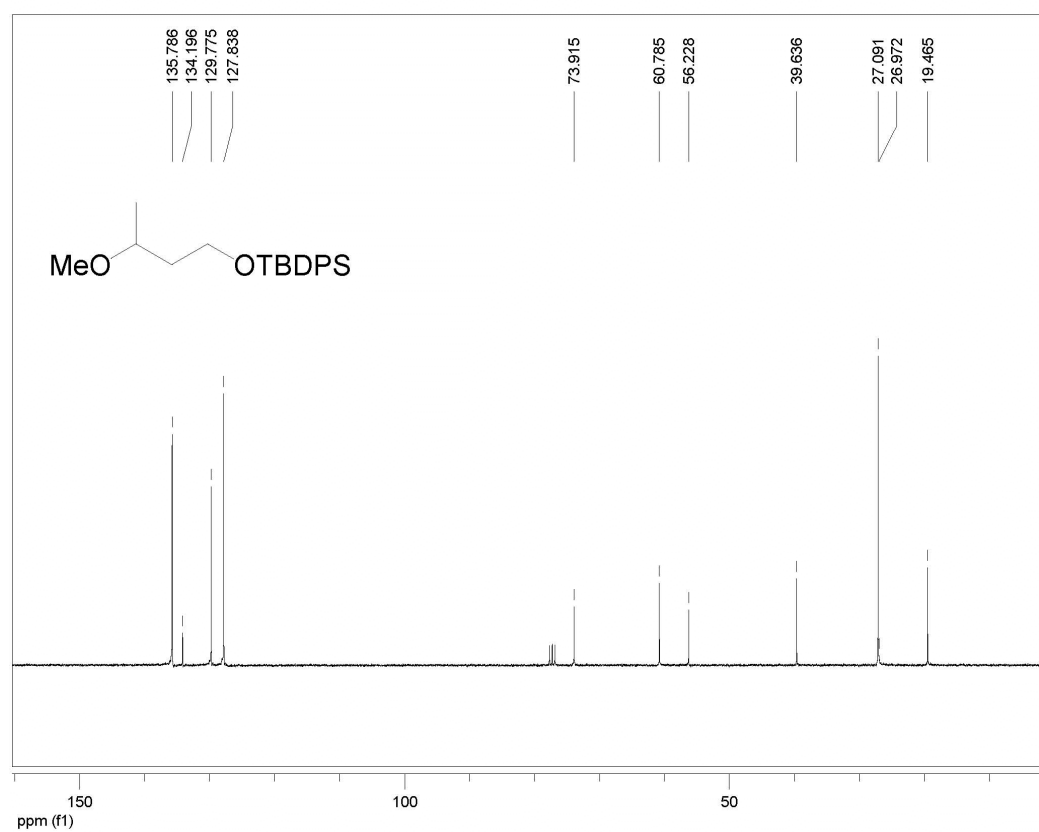
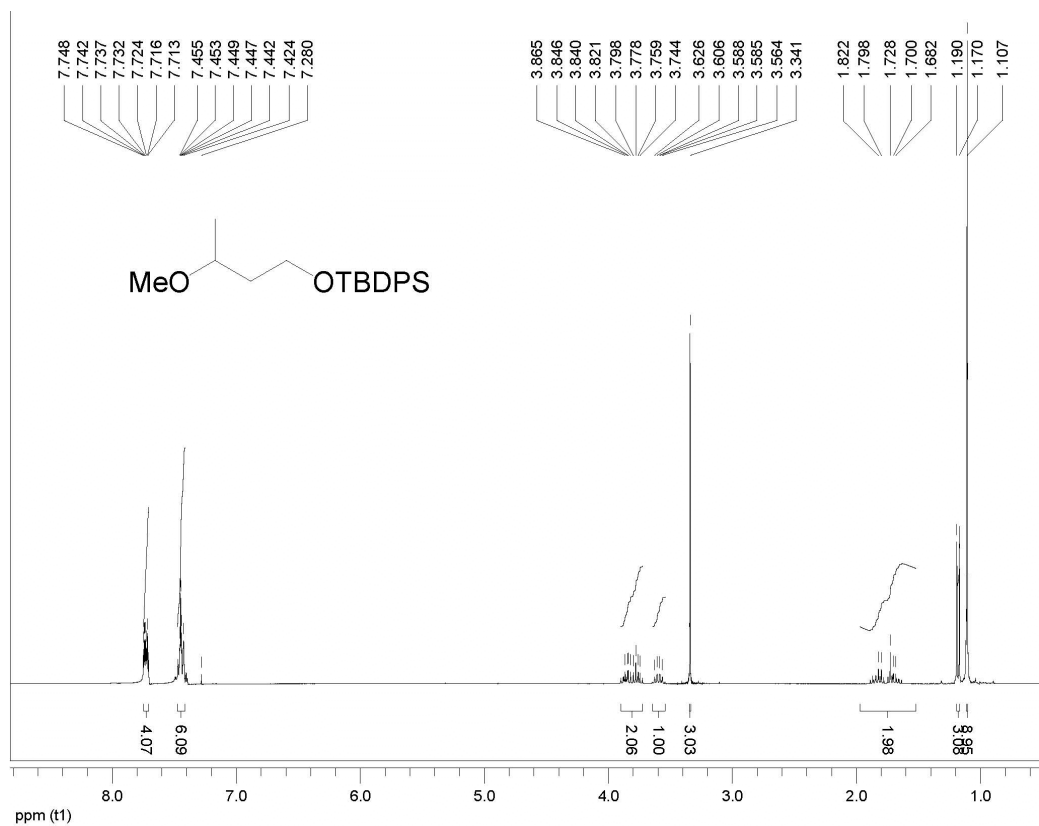


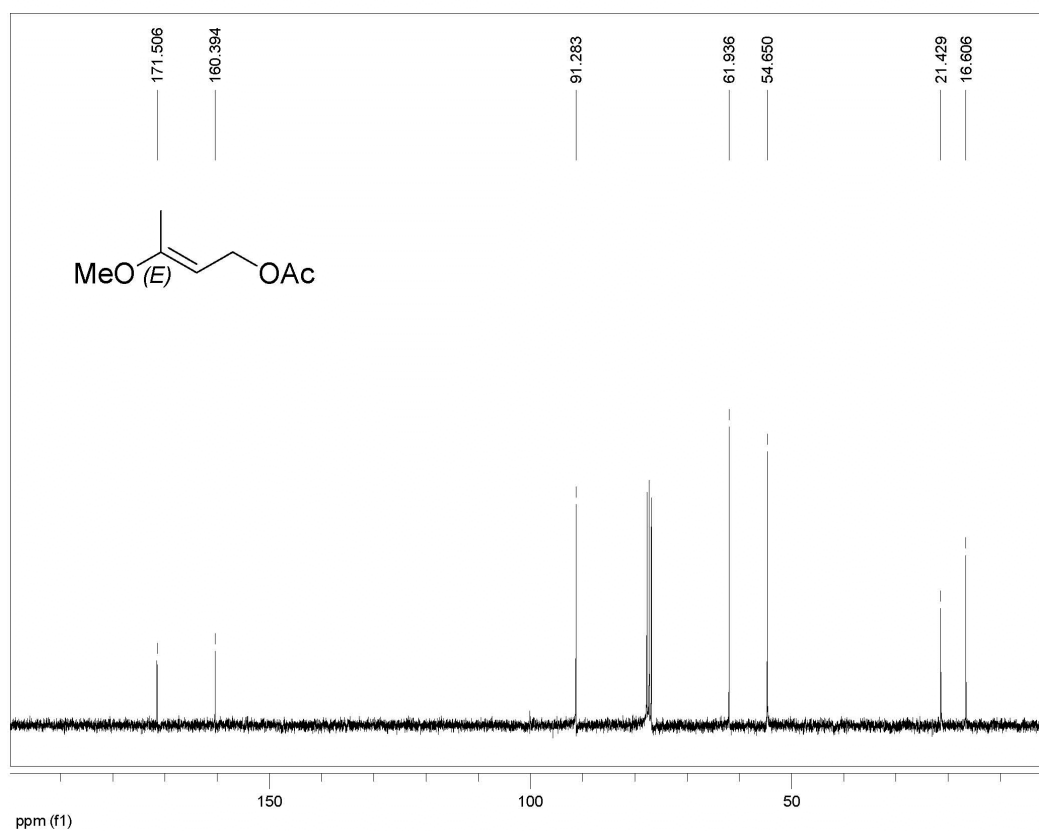
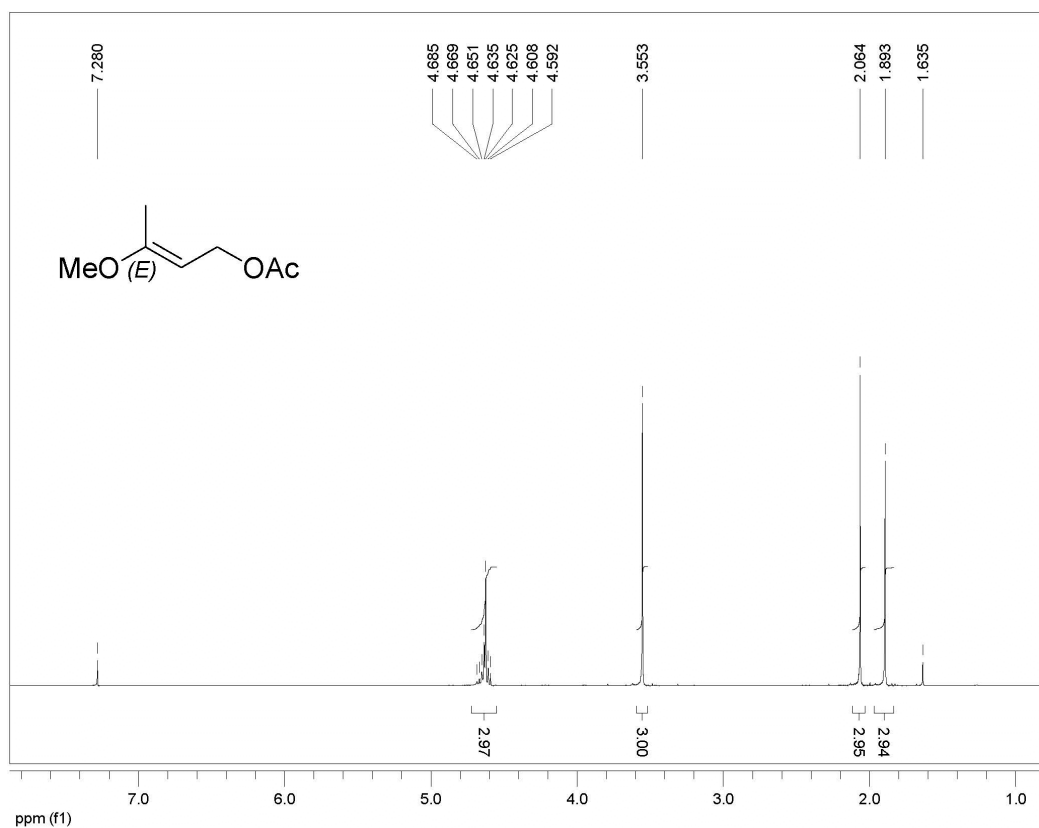


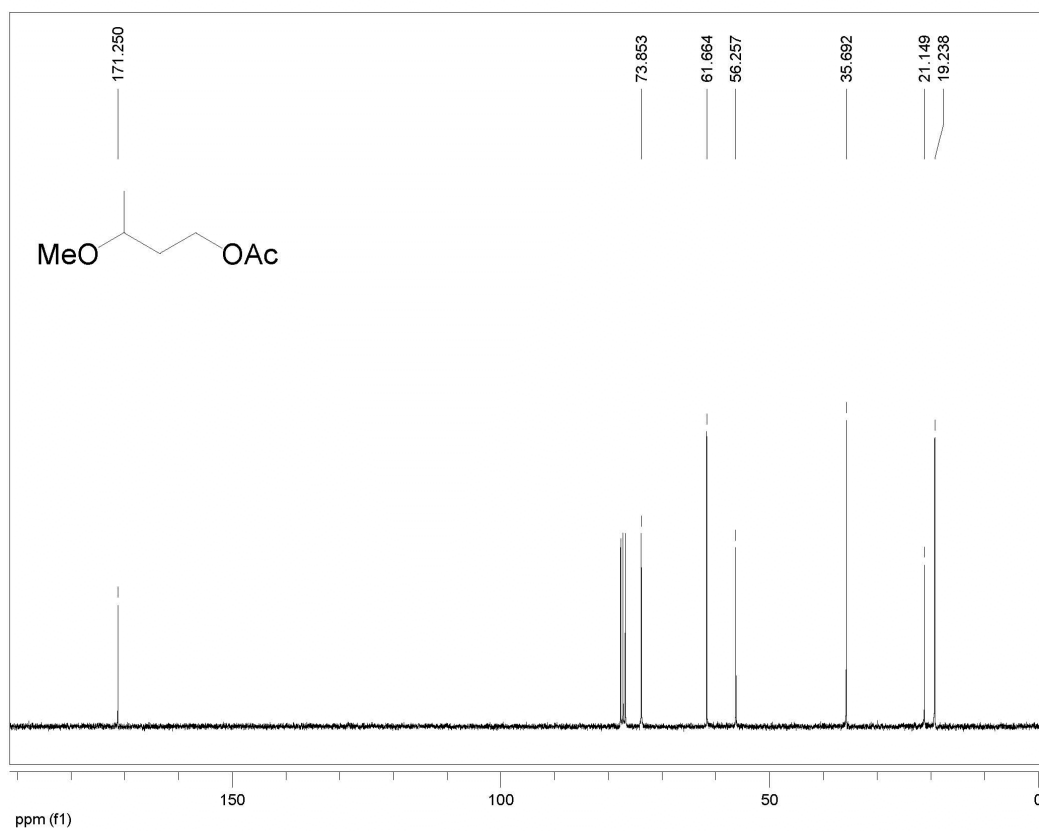
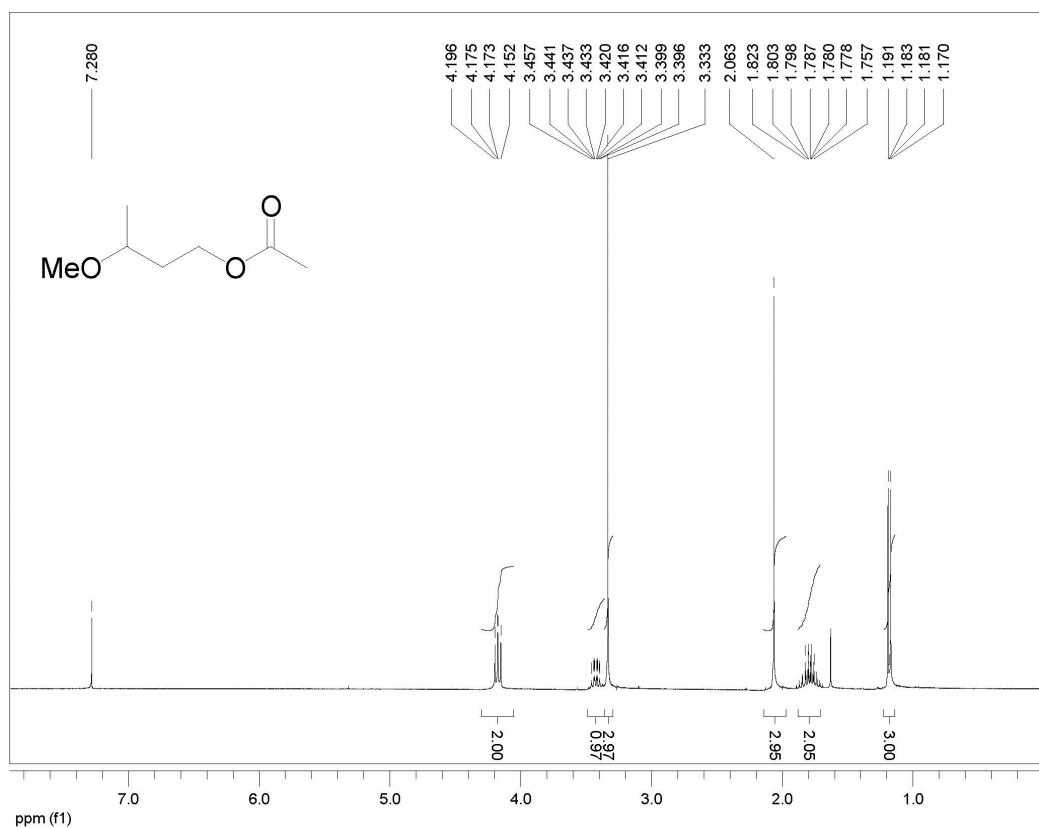


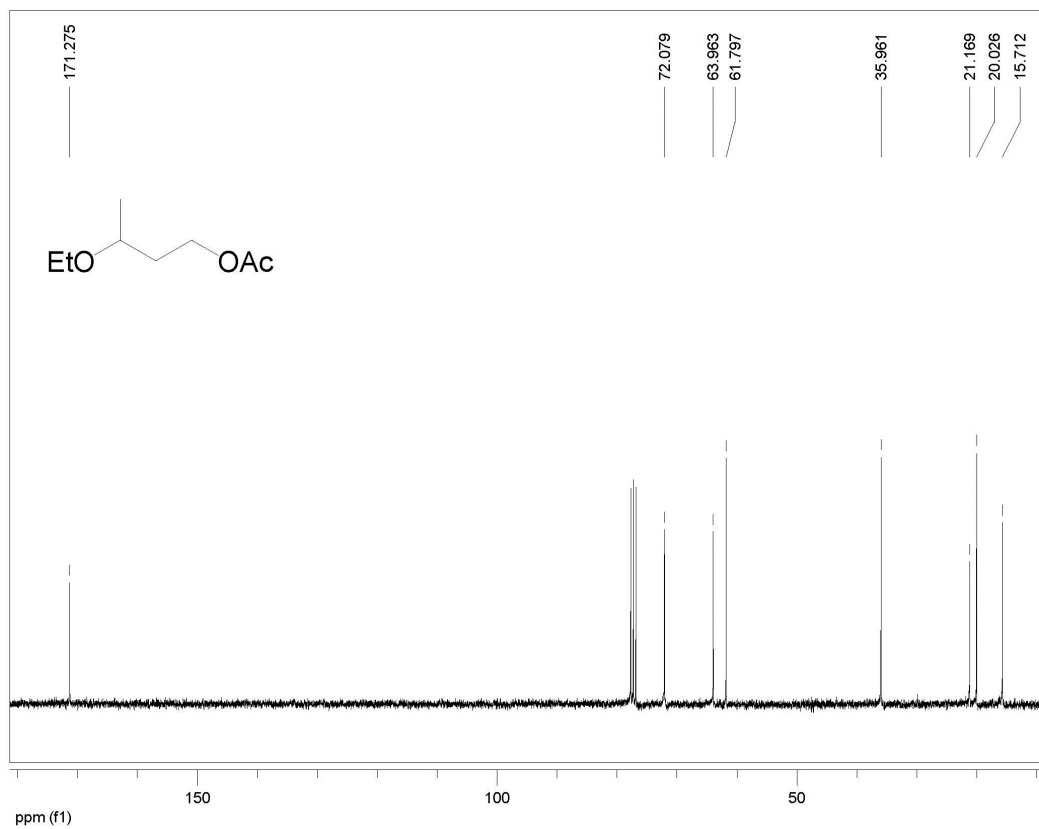
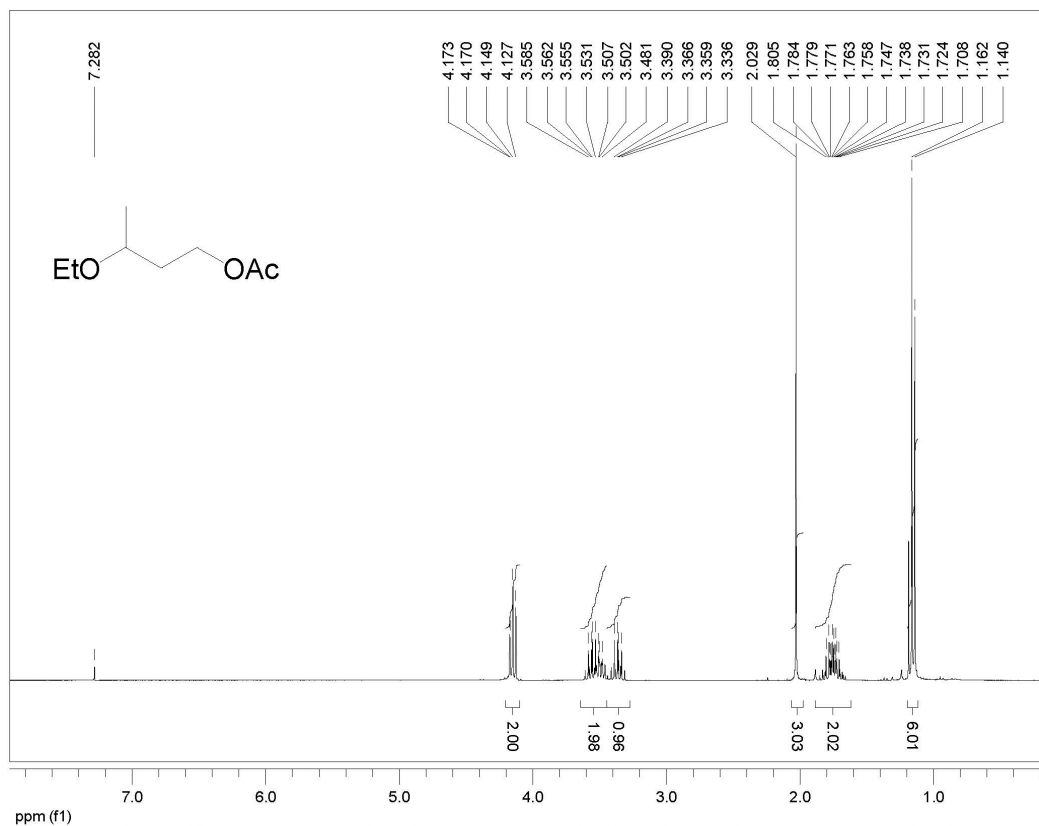




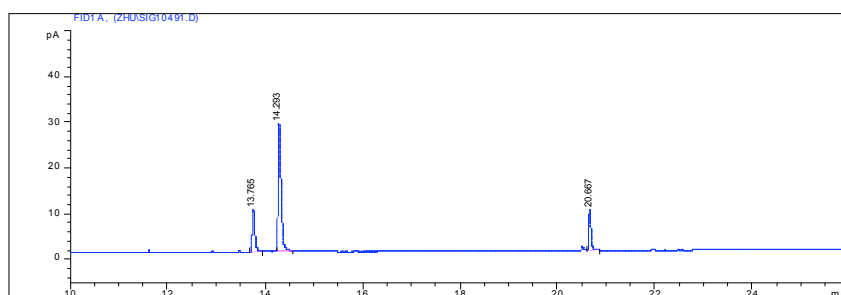
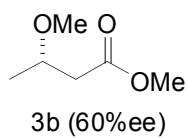
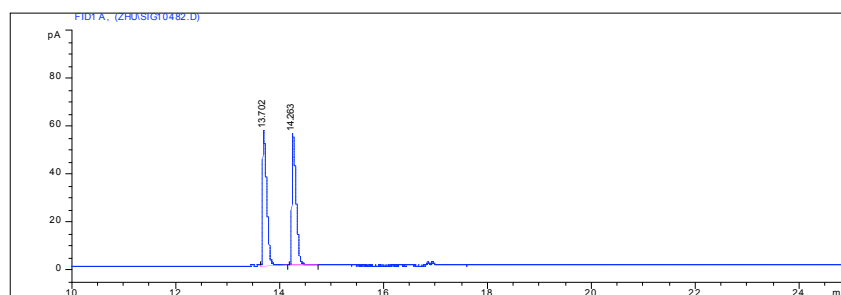
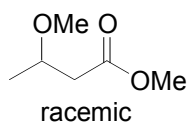
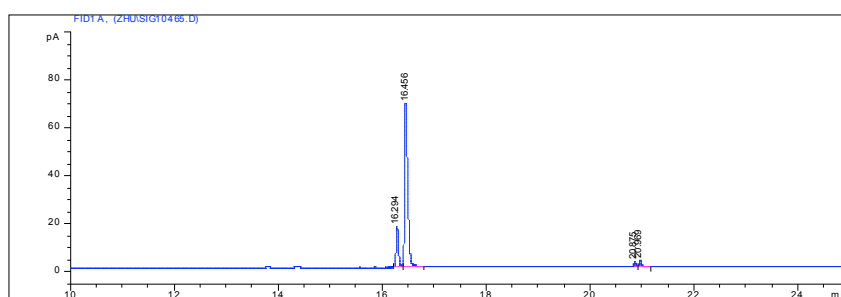
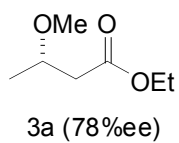
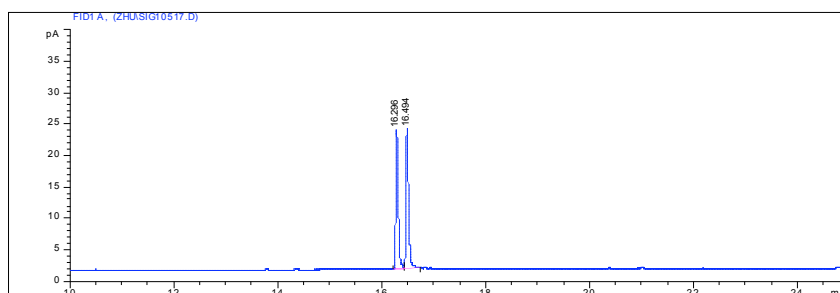
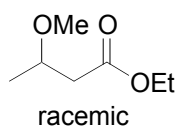


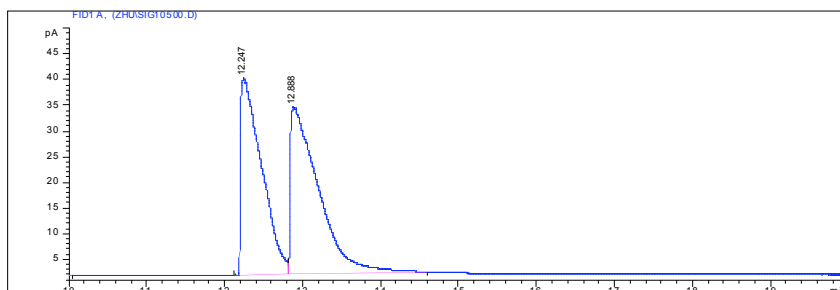
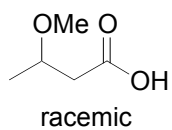
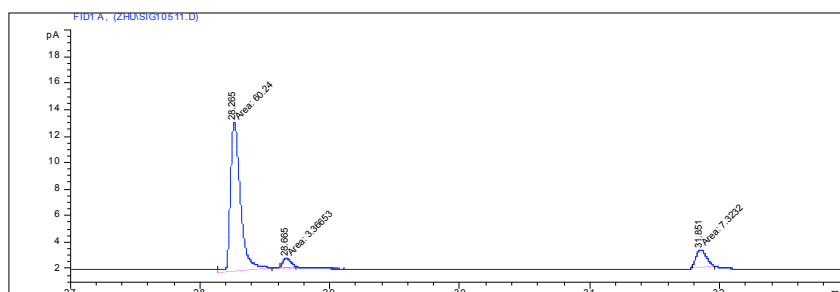
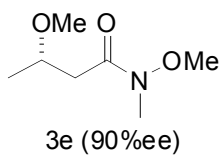
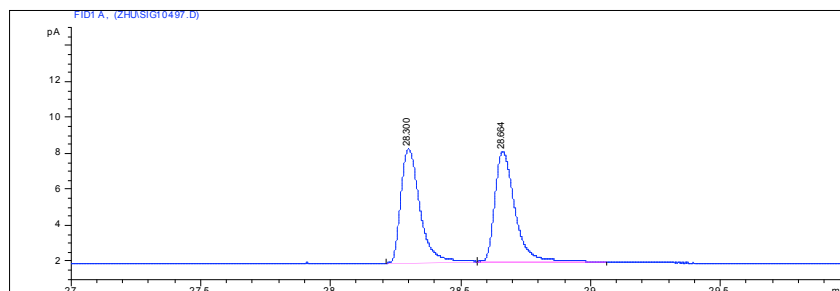
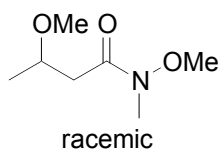
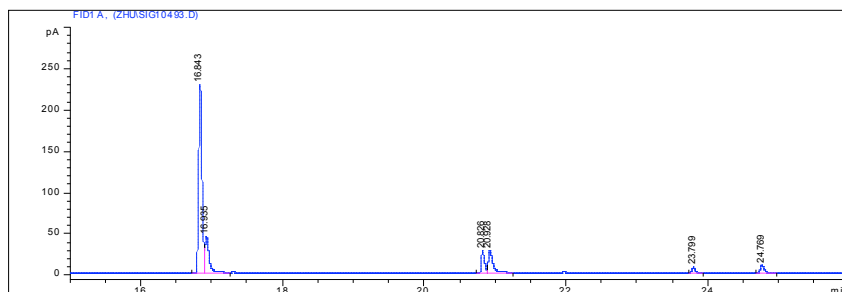
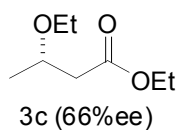
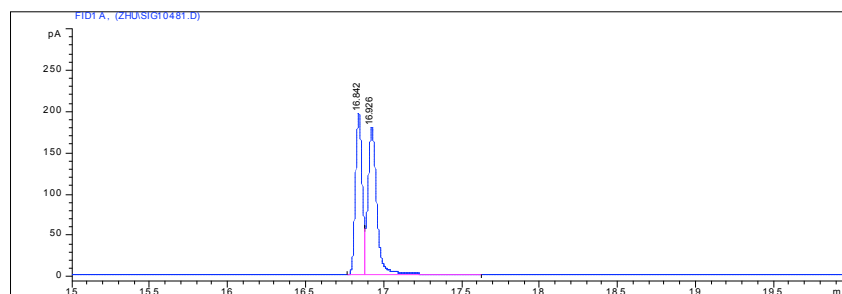
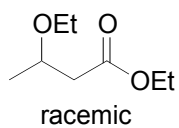


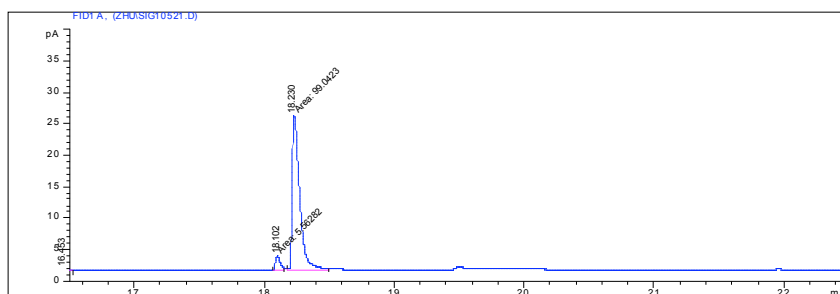
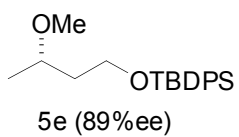
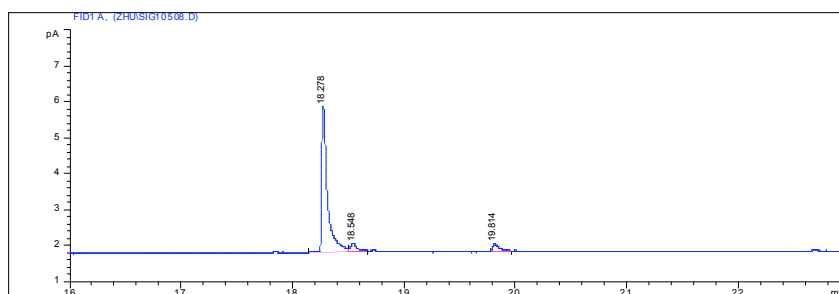
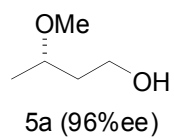
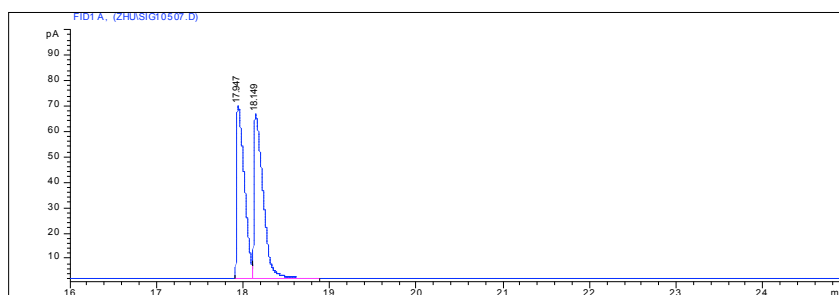
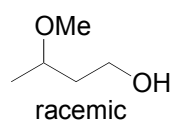
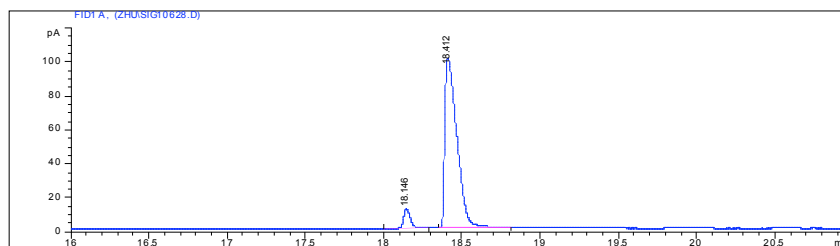
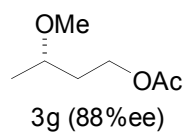
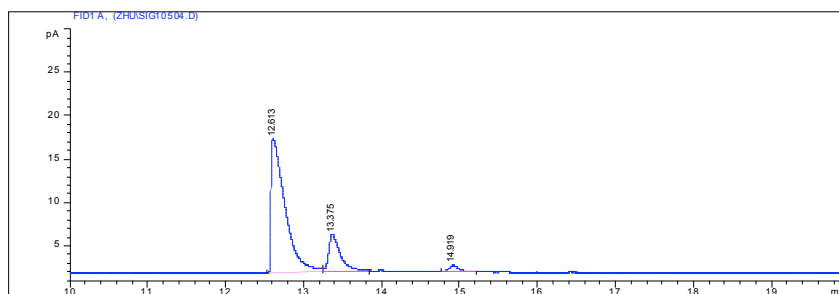


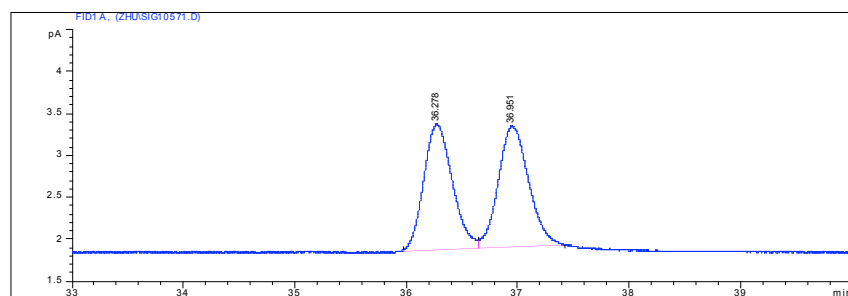
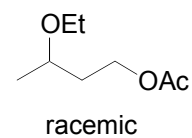
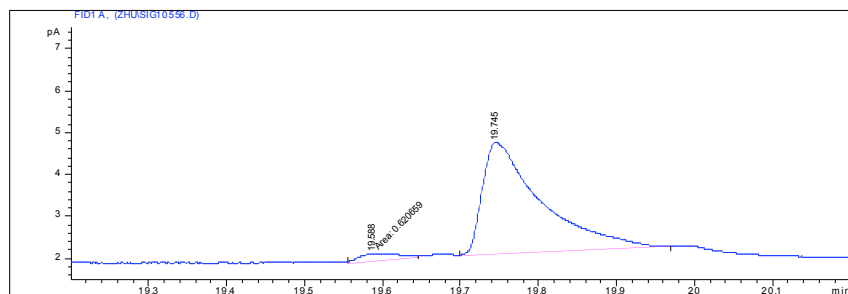
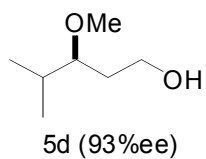
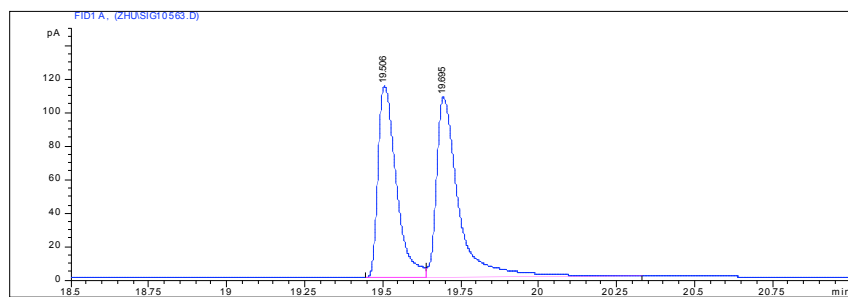
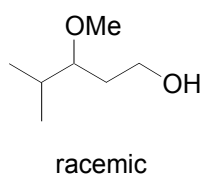
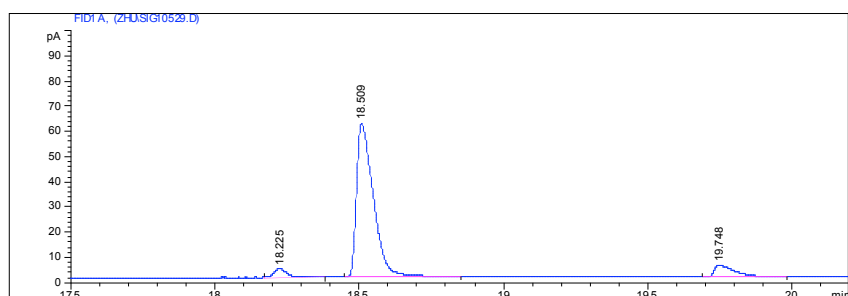
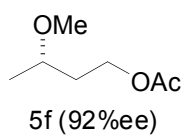
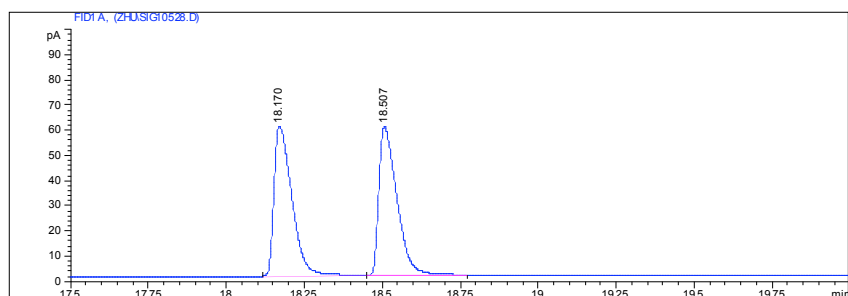
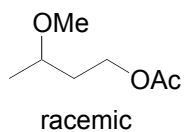


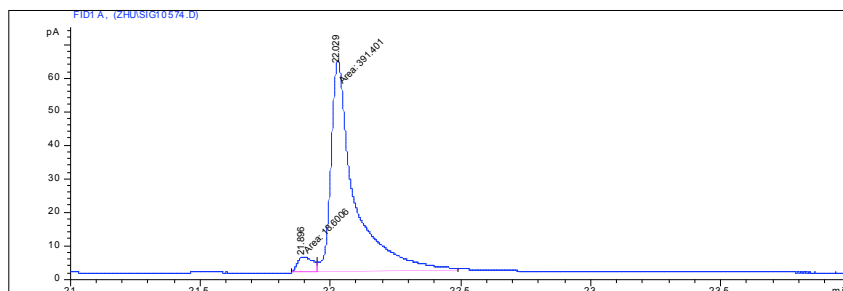
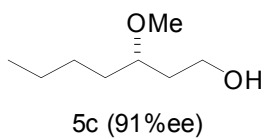
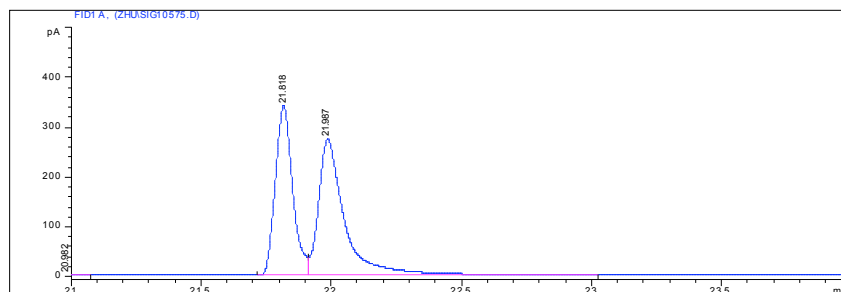
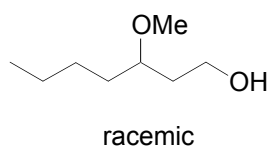
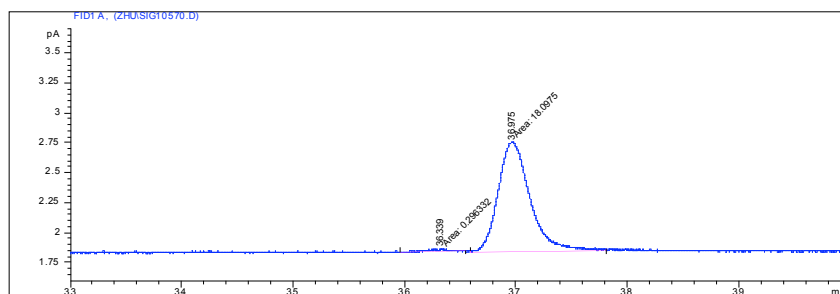
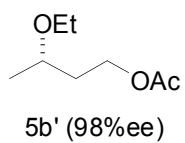
GC data:











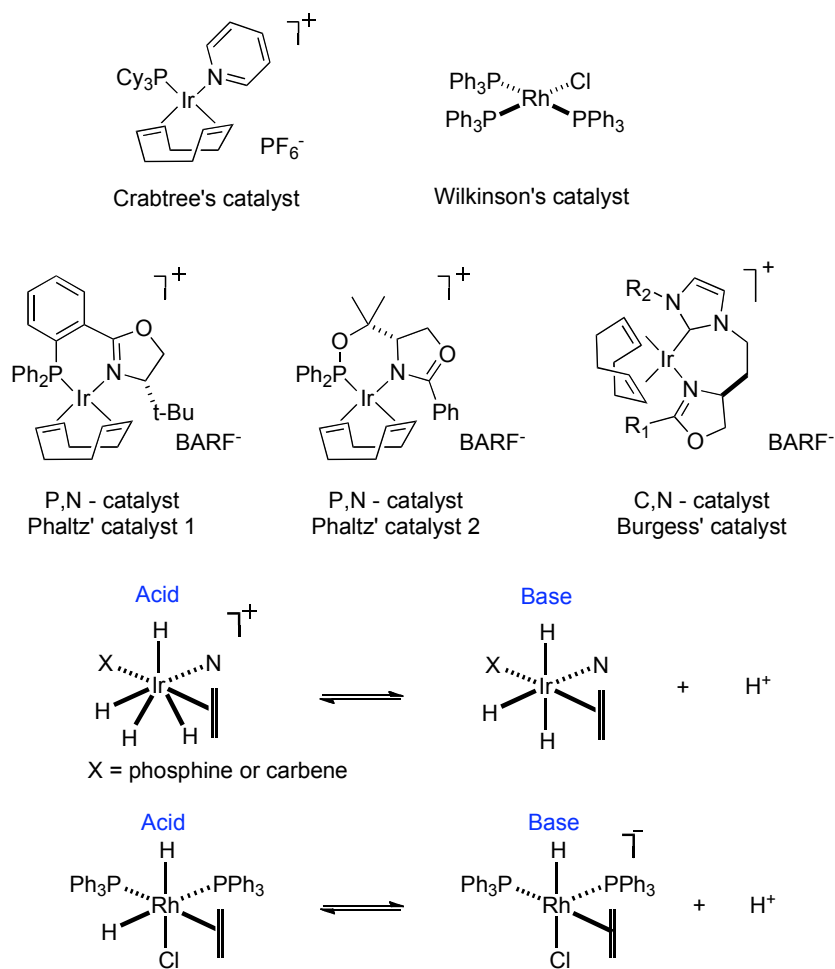
Computational Details

All calculations were performed using the Gaussian 03¹ implementation of Tao-Perdew-Staroverov-Scuseria (TPSS) density functional theory (DFT).² As a third generation of density functional, TPSS is generally superior to all previously developed nonempirical functionals, and virtually matches in accuracy the most popular functional-B3LYP.³⁻⁶

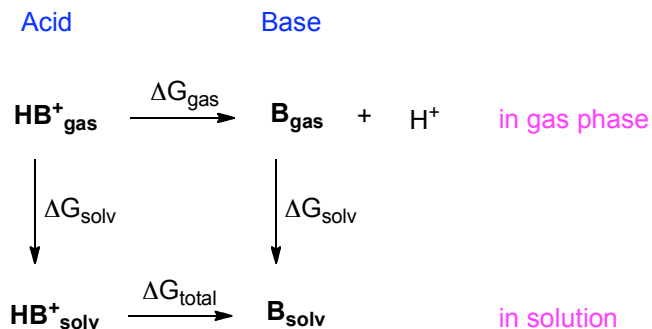
The basis sets for transition metals (Ir, Rh, Pt and Ni) were Stuttgart/Dresden (SDD) with the effective core potential (ECP)⁷ while those for phosphorus and chlorine were LANL2DZ plus a *d*-polarization and a *p*-diffuse function⁸ with ECP.^{9,10} Further, an *f*-polarization function was also added to the second- and third-row transition metals.¹¹ 6-31++G(d',p') basis sets were used for all C, N and O in the directly-bound conjugated ligand systems, such as imidazolidine, oxazoline and pyridine, and hydrides, dihydrogen. The same basis sets were also applied to all atoms in ethene¹²⁻¹⁴ while 6-31G was used for the rest atoms.¹² In addition, density fitting functions were included to accelerate the computation with DFT.^{15,16} Density fitting functions can be included for this pure DFT—and only pure DFT—to save tremendous computational expense by expanding the density in a set of atom-centered functions when computing the Coulombic interaction instead of computing all of the two-electron integrals.^{15,16} A comparison of TPSS with or without density fitting functions included for an organometallic reaction shows only marginal difference for both relative energies and structural parameters.¹⁷ TPSS reproduces these properties at least as precisely as B3LYP. Especially, TPSS can recognize relatively weak interactions (such as agostic interactions) very well while B3LYP significantly underestimates them. Furthermore, using smaller basis sets for the atoms far from the reaction center does not degrade the computational precision and accuracy significantly but can accelerate the calculations considerably.¹⁷

All structures were fully optimized in dichloromethane solution and frequency analyses were performed to ensure a minimum was achieved. The thermodynamic functions, including enthalpies, entropies and free energies, were calculated at 298.15 K and 1 atm. The solvation free energies were computed by using polarizable conductor calculation model (CPCM).^{18,19}

The catalysts investigated in the calculations are seen below. The acid-base balance is shown in Scheme S1. The pK_a values for the ethene and hydrides coordinated intermediates in acetonitrile and dichloromethane solution are listed in Tables S1 and S2, respectively. The calculation for pK_a is based on the Born-Haber Cycle and the corresponding methods are shown in Scheme S2 and Equations 1-5.



Scheme D-1. The acid-base balance.



Scheme D-2. The Born-Haber cycle

$$\Delta G_{\text{gas}} = G_{\text{gas}}(\text{base}) - G_{\text{gas}}(\text{acid}) \quad (1)$$

$$\Delta G_{\text{total}} = \Delta G_{\text{gas}} + [\Delta G_{\text{solv}}(\text{acid}) - \Delta G_{\text{solv}}(\text{base})] \quad (2)$$

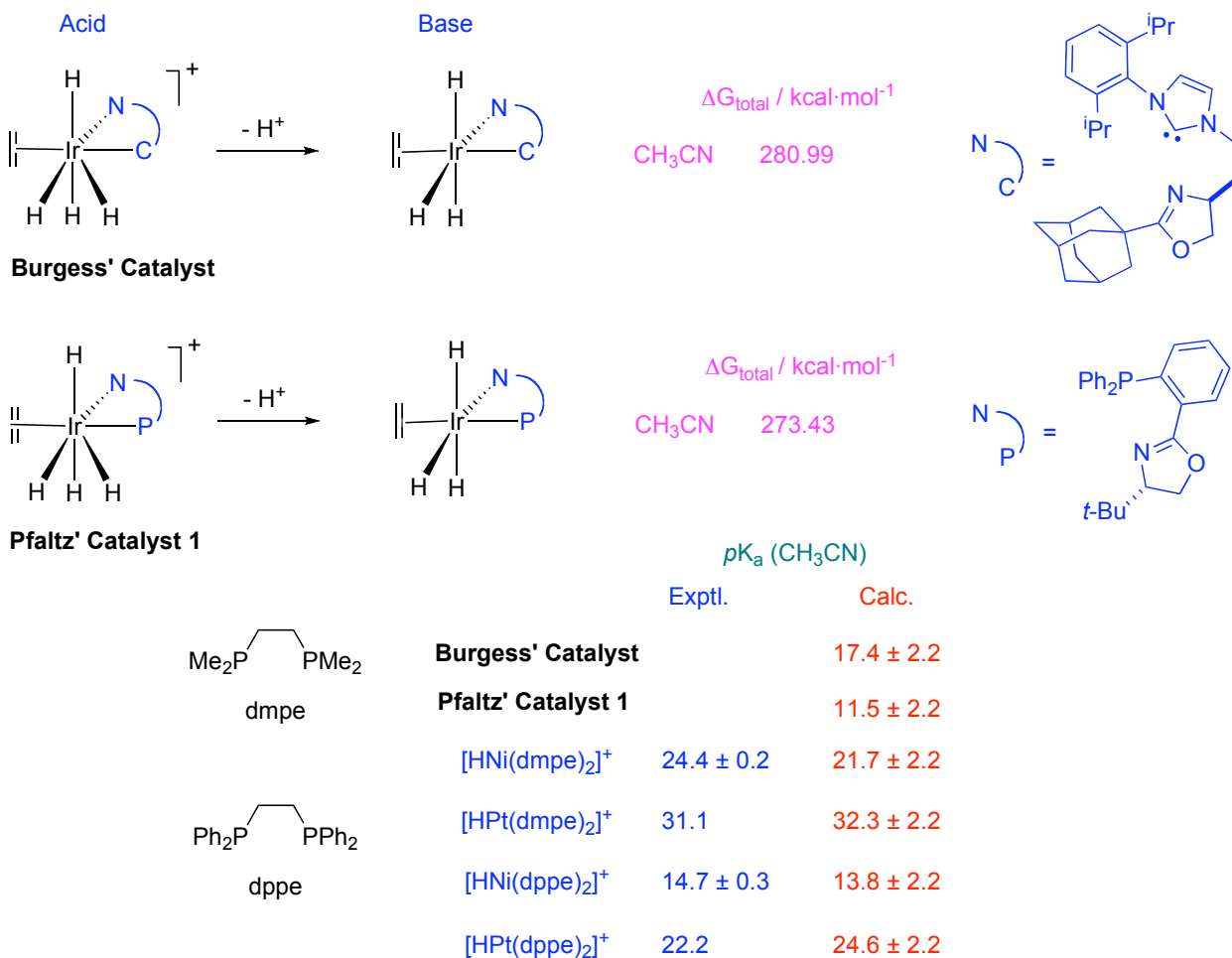
$$\text{Set } \Delta \Delta G_{\text{total}} = \Delta G_{\text{total}}(2) - \Delta G_{\text{total}}(1) \quad (3)$$

$$pK_a = 2.3026 \Delta G_{\text{total}} / RT$$

$$R = 1.987 \text{ cal/mol/K} \quad (4)$$

$$T = 298.15 \text{ K}$$

$$\text{Then } pK_a(2) = pK_a(1) + 2.3026 \Delta \Delta G_{\text{total}} / RT \quad (5)$$



Scheme D-3. Selected examples of calculated pK_a values in acetonitrile.

Table D-1. Calculated pK_a in acetonitrile.

Catalyst	Acid		Base		ΔG_{total} (kcal/mol)	pK_a (expl.)	pK_a (calc.)
	G_{gas} (Hartree) ^a	ΔG_{solv} (kcal/mol)	G_{gas} (Hartree) ^a	ΔG_{solv} (kcal/mol)			
$[\text{HNi}(\text{dmpe})_2]^+$	-673.727152	-11.96	-673.313930	17.98	289.24	24.4 \pm 0.2 ²⁰	21.7 \pm 2.2
$[\text{HPt}(\text{dmpe})_2]^+$	-630.694836	-9.68	-630.278621	19.34	290.20	31.1 ²¹	32.3 \pm 2.2
$[\text{HNi}(\text{dppe})_2]^+$	-2207.251396	15.93	-2206.844821	39.23	278.43	14.7 \pm 0.3 ²⁰	13.8 \pm 2.2
$[\text{HPt}(\text{dppe})_2]^+$	-2155.752957	18.49	-2155.319423	39.60	293.16	22.2 ²⁰	24.6 \pm 2.2
Crabtree's	-1145.473993	-10.09	-1145.076729	15.59	274.97	-	11.3 \pm 2.2
Wilkinson's	-1608.110244	8.51	-1607.571089	-18.01	311.80	-	36.1 \pm 2.2
Burgess'	-1592.227152	-18.12	-1591.817578	5.86	280.99	-	17.4 \pm 2.2
Pfaltz' 1	-1289.821847	-15.32	-1289.420063	5.99	273.43	-	11.5 \pm 2.2
Pfaltz' 2	-1325.770711	-17.62	-1325.373954	4.34	270.93	-	9.8 \pm 2.2

^a 1 Hartree = 627.5095 kcal/mol.

For example, based on equations 1-5:

$$\begin{aligned}\Delta G_{\text{total}}(\text{Burgess'}) &= \Delta G_{\text{gas}} + [\Delta G_{\text{solv}}(\text{acid}) - \Delta G_{\text{solv}}(\text{base})] \\ &= (-1591.817578 + 1592.227152) \times 627.5095 + (5.86 + 18.12) = 283.30 \text{ kcal/mol}\end{aligned}$$

So, if choose metal hydride $[\text{HNi}(\text{dmpe})_2]^+$ as the reference,

$$\begin{aligned}\Delta \Delta G_{\text{total}} &= \Delta G_{\text{total}}(\text{Burgess's}) - \Delta G_{\text{total}}([\text{HNi}(\text{dmpe})_2]^+) \\ &= 283.30 - 289.24 = -5.94 \text{ kcal/mol}\end{aligned}$$

The calculated pK_a value of metal hydride from Burgess's catalyst will be:

$$\begin{aligned}pK_a(\text{Burgess's}) &= pK_a([\text{HNi}(\text{dmpe})_2]^+) + 2.3026 \Delta \Delta G_{\text{total}} / RT \\ &= 24.4 - 2.3026 \times 5.94 \times 1000 / 1.987 / 298.15 = 20.0\end{aligned}$$

Here, the calculated pK_a 's listed were calculated first as pK_a differences. These values were then compared with the experimental pK_a 's for each reference compound to give a set of pK_a values against the reference. The values quoted are averaged from this procedure, where the errors shown are standard deviation.^{19,20}

Table D-2. Calculated pK_a in dichloromethane.

Catalyst	Acid		Base		ΔG_{total} (kcal/mol)	pK_a^a (relative)
	G_{gas} (Hartree)	ΔG_{solv} (kcal/mol)	G_{gas} (Hartree)	ΔG_{solv} (kcal/mol)		
Crabtree's	-1145.473993	-18.63	-1145.076729	4.87	273.433277	1.4
Wilkinson's	-1608.110244	8.51	-1607.571089	-18.01	270.928787	30.0
Burgess'	-1592.227152	-18.12	-1591.817578	5.86	272.786934	7.4
Pfaltz' 1	-1289.821847	-15.32	-1289.420063	5.99	311.804884	1.8
Pfaltz' 2	-1325.770711	-17.62	-1325.373954	4.34	280.991576	0.0

^a The pK_a for Pfaltz' catalyst 2 is set to 0.

Table D-3. Cartesian coordinates and electronic energies for all species listed in Tables S1, S2.**1. Crabtree's catalyst****Acid E = -1146.068380600 Hartree**

Ir	1.007947	-1.422781	-0.186460
P	-0.911763	0.058889	-0.122330
C	-1.055132	0.918301	1.573613
C	0.075800	1.957506	1.782204
C	0.114372	2.440916	3.249886
C	-1.246669	3.013422	3.692101
C	-2.380022	1.998481	3.448665
C	-2.422853	1.530725	1.973935
H	-0.866603	0.074311	2.263915
H	1.049290	1.534926	1.494722
H	-0.101267	2.823272	1.123573
H	0.906209	3.197326	3.366958
H	0.384312	1.592407	3.903765
H	-1.211413	3.295949	4.755203
H	-1.455493	3.937606	3.125891
H	-2.236849	1.121270	4.103694
H	-3.352958	2.437774	3.717184
H	-3.234405	0.802147	1.845579
H	-2.656079	2.391607	1.330757
C	-0.999212	1.326397	-1.545587
C	-1.982948	2.507657	-1.329120
C	-2.120061	3.342359	-2.624328
C	-0.755992	3.881194	-3.093858
C	0.257939	2.733484	-3.261070
C	0.379557	1.878675	-1.978539
H	-1.381115	0.702100	-2.375588
H	-2.972790	2.159903	-1.006549
H	-1.593402	3.161335	-0.531636
H	-2.820968	4.172228	-2.445360
H	-2.565805	2.716494	-3.416828
H	-0.867858	4.429479	-4.041509
H	-0.373949	4.604241	-2.352248
H	-0.057593	2.083538	-4.095758
H	1.249312	3.132160	-3.528908
H	1.067762	1.042165	-2.157097
H	0.809254	2.487393	-1.165372
C	-2.441172	-1.064222	-0.366408
C	-2.681317	-1.974220	0.865987

C	-3.762048	-3.039095	0.569896
C	-5.078054	-2.393193	0.097482
C	-4.833236	-1.484091	-1.121053
C	-3.763840	-0.403112	-0.830729
H	-2.093536	-1.710179	-1.191999
H	-1.746693	-2.477370	1.158900
H	-3.004602	-1.364076	1.725147
H	-3.930560	-3.645887	1.473002
H	-3.388163	-3.725011	-0.209763
H	-5.814413	-3.172040	-0.152284
H	-5.512633	-1.798161	0.919681
H	-4.502622	-2.098361	-1.976596
H	-5.767622	-0.990321	-1.429359
H	-3.602014	0.187377	-1.744171
H	-4.147404	0.284100	-0.060280
N	2.773182	-0.075311	0.177811
C	3.292792	0.115868	1.421797
H	2.726162	-0.313804	2.246647
C	4.479745	0.813641	1.660247
H	4.836872	0.927504	2.683098
C	5.185498	1.349282	0.573697
H	6.114711	1.898055	0.725803
C	4.665772	1.155266	-0.712893
H	5.172594	1.544207	-1.595273
C	3.471525	0.443794	-0.866928
H	3.045493	0.271010	-1.852552
H	0.967627	-1.498078	1.617562
H	-0.088067	-2.483557	-0.619548
H	0.466208	-2.129085	1.355452
H	1.000327	-1.004618	-1.727266
C	2.443105	-2.777194	-1.256597
C	2.471178	-3.121285	0.101327
H	1.869271	-3.368386	-1.967386
H	3.240906	-2.170087	-1.683974
H	1.916332	-3.988333	0.457951
H	3.288100	-2.779909	0.738107

Base E = -1145.661164160 Hartree

Ir	1.034080	-1.389419	-0.257848
P	-0.868022	0.034415	-0.126630

C	-1.061717	0.883978	1.574871	H	-3.798322	-3.730578	1.469470
C	0.060801	1.925710	1.802996	H	-3.261998	-3.773693	-0.217186
C	0.104896	2.380793	3.278549	H	-5.710893	-3.298822	-0.135903
C	-1.258042	2.935367	3.739491	H	-5.435977	-1.924034	0.945816
C	-2.386017	1.916709	3.481504	H	-4.445657	-2.168079	-1.960303
C	-2.429056	1.476578	1.998220	H	-5.744870	-1.107501	-1.393242
H	-0.848568	0.026647	2.238335	H	-3.612252	0.139390	-1.718770
H	1.031462	1.505277	1.506075	H	-4.145740	0.209563	-0.030476
H	-0.117748	2.806434	1.162470	N	2.770595	-0.068365	0.130857
H	0.892552	3.140598	3.412611	C	3.256353	0.086657	1.392048
H	0.381148	1.519081	3.911639	H	2.646067	-0.366101	2.172142
H	-1.221379	3.202410	4.808257	C	4.447392	0.763189	1.676836
H	-1.477310	3.866954	3.187526	H	4.778909	0.851606	2.711649
H	-2.228089	1.028156	4.117982	C	5.192257	1.310316	0.621911
H	-3.360639	2.344094	3.769230	H	6.124806	1.843174	0.810970
H	-3.235000	0.742164	1.861570	C	4.707383	1.146202	-0.683447
H	-2.682086	2.349335	1.377070	H	5.247750	1.541984	-1.543568
C	-1.043906	1.348611	-1.510718	C	3.506928	0.455366	-0.884225
C	-2.051114	2.501241	-1.274204	H	3.097116	0.290950	-1.879248
C	-2.213842	3.363256	-2.548439	H	0.757763	-1.518798	1.385493
C	-0.862121	3.938755	-3.014115	H	1.004562	-0.983944	-1.876182
C	0.176710	2.816358	-3.204843	H	-0.063912	-2.496723	-0.551062
C	0.320351	1.940545	-1.939994	C	2.443116	-2.792375	-1.117350
H	-1.408154	0.733218	-2.355828	C	2.326217	-3.038538	0.287740
H	-3.032260	2.125199	-0.954743	H	1.953981	-3.455045	-1.829949
H	-1.676959	3.148830	-0.463449	H	3.335724	-2.294943	-1.504549
H	-2.931572	4.177457	-2.354759	H	1.749101	-3.890140	0.646194
H	-2.646844	2.743558	-3.353826	H	3.130367	-2.725423	0.958026
H	-0.989857	4.507728	-3.949519				
H	-0.492601	4.652811	-2.256451				
H	-0.129334	2.175718	-4.051035				
H	1.156992	3.244619	-3.472695				
H	1.021441	1.116064	-2.125367				
H	0.736430	2.547863	-1.117432				
C	-2.403273	-1.087992	-0.360781				
C	-2.604500	-2.011468	0.868013				
C	-3.651369	-3.107249	0.572249				
C	-4.992661	-2.500891	0.114117				
C	-4.788781	-1.570173	-1.097441				
C	-3.747041	-0.462915	-0.807674				
H	-2.048547	-1.725954	-1.189111				
H	-1.642703	-2.465529	1.146618				
H	-2.948655	-1.416194	1.731399				

2. Wilkinson's catalyst

Acid E = -1608.64423489 Hartree

Rh	-0.003829	-0.150191	-0.215730
P	-2.358400	0.012168	0.028421
C	-2.928419	0.345273	1.781367
C	-4.165375	-0.132726	2.259870
H	-4.801476	-0.744269	1.620359
C	-4.583788	0.160364	3.568024
H	-5.538734	-0.228196	3.925943
C	-3.778461	0.941078	4.411385
H	-4.104342	1.165554	5.428340
C	-2.545433	1.421456	3.942054

H	-1.905659	2.021305	4.591607	H	4.171584	-0.437310	5.482518
C	-2.118773	1.118780	2.639769	C	4.493832	0.526432	3.567697
H	-1.146954	1.470479	2.292012	H	5.351073	1.109334	3.909205
C	-3.497552	-1.354653	-0.546125	C	4.055857	0.653588	2.239404
C	-3.029101	-2.684663	-0.521801	H	4.578180	1.338112	1.571130
H	-2.003989	-2.891962	-0.204808	C	3.103419	1.649232	-0.575803
C	-3.873691	-3.736175	-0.915835	C	2.341987	2.835537	-0.567582
H	-3.495609	-4.759615	-0.896030	H	1.296285	2.796436	-0.258486
C	-5.186447	-3.474762	-1.336771	C	2.911046	4.055663	-0.965240
H	-5.838202	-4.293781	-1.646176	H	2.303610	4.962201	-0.954513
C	-5.659108	-2.151640	-1.361595	C	4.250142	4.107250	-1.382914
H	-6.678866	-1.937799	-1.686868	H	4.690901	5.054124	-1.699105
C	-4.821806	-1.096061	-0.968870	C	5.018176	2.931795	-1.397260
H	-5.201161	-0.073753	-0.996105	H	6.059791	2.959994	-1.721842
C	-3.042672	1.487425	-0.905237	C	4.451548	1.711821	-0.994764
C	-3.241259	1.395675	-2.301234	H	5.059147	0.806420	-1.014221
H	-3.077074	0.446986	-2.815613	Cl	0.312832	-2.615070	0.275695
C	-3.671897	2.509695	-3.038408	H	-0.111035	1.411800	-0.131689
H	-3.824747	2.416407	-4.114996	H	0.013994	0.001582	1.341666
C	-3.906611	3.735279	-2.393939	C	0.114773	0.457667	-2.447751
H	-4.242266	4.601363	-2.966454	C	-0.130238	-0.904488	-2.405013
C	-3.711433	3.835796	-1.007744	H	-0.687670	1.177117	-2.603922
H	-3.897375	4.781196	-0.495071	H	1.121015	0.847503	-2.599667
C	-3.282931	2.721306	-0.268105	H	-1.138903	-1.301475	-2.521460
H	-3.142667	2.816212	0.809106	H	0.673673	-1.635719	-2.471947
P	2.331961	0.049115	0.018887	Base E = -1608.09285965 Hartree			
C	3.323903	-1.237268	-0.898709	Rh	0.008362	-0.555366	-0.332793
C	3.518586	-1.113292	-2.292014	P	-2.192852	-0.045149	0.015018
H	3.159691	-0.229283	-2.822032	C	-2.769385	0.368061	1.770885
C	4.192207	-2.113249	-3.009859	C	-4.117941	0.252245	2.169538
H	4.339168	-1.998189	-4.085154	H	-4.863537	-0.121606	1.467482
C	4.674447	-3.253245	-2.346451	C	-4.516758	0.594976	3.471953
H	5.197139	-4.032000	-2.904200	H	-5.564905	0.486956	3.760950
C	4.476825	-3.386734	-0.963581	C	-3.573494	1.067115	4.399567
H	4.840021	-4.272930	-0.440820	H	-3.882060	1.328474	5.414414
C	3.802335	-2.389060	-0.242785	C	-2.228922	1.187325	4.013671
H	3.644806	-2.512617	0.827838	H	-1.481518	1.542221	4.726670
C	2.943254	-0.082560	1.782296	C	-1.831766	0.836207	2.712293
C	2.275550	-0.948821	2.674681	H	-0.782712	0.899140	2.417207
H	1.417216	-1.526392	2.325630	C	-3.491854	-1.335453	-0.477106
C	2.724298	-1.077710	3.998765	C	-3.080623	-2.683804	-0.404993
H	2.201947	-1.754868	4.676779	H	-2.052554	-2.919229	-0.104056
C	3.830851	-0.340411	4.450156				

C	-3.969729	-3.715897	-0.750530
H	-3.632591	-4.752870	-0.690215
C	-5.270525	-3.418593	-1.189475
H	-5.955686	-4.222457	-1.469608
C	-5.682449	-2.077912	-1.281025
H	-6.688756	-1.834535	-1.631593
C	-4.799727	-1.043991	-0.924916
H	-5.130375	-0.006617	-1.008933
C	-2.857623	1.460094	-0.897263
C	-3.112222	1.386189	-2.288409
H	-3.037138	0.425492	-2.801593
C	-3.473967	2.528720	-3.020234
H	-3.665508	2.441967	-4.092319
C	-3.586794	3.775053	-2.382457
H	-3.867381	4.663840	-2.951622
C	-3.330315	3.864562	-1.002525
H	-3.416593	4.826154	-0.490580
C	-2.968108	2.722695	-0.271413
H	-2.771458	2.813048	0.798328
P	2.212457	0.051625	0.001145
C	3.492159	-0.827460	-1.063505
C	3.902385	-0.322032	-2.318360
H	3.577887	0.669133	-2.640200
C	4.732123	-1.076209	-3.164759
H	5.038417	-0.660521	-4.127804
C	5.163250	-2.355357	-2.777667
H	5.807306	-2.943029	-3.435633
C	4.743023	-2.877157	-1.542460
H	5.051031	-3.879418	-1.237087
C	3.912024	-2.127053	-0.697810
H	3.567319	-2.564874	0.238695
C	2.906996	-0.250460	1.725996
C	2.423235	-1.379502	2.424338
H	1.675988	-2.024370	1.948743
C	2.892997	-1.669198	3.715608
H	2.510269	-2.549559	4.236651
C	3.831907	-0.830199	4.339106
H	4.185681	-1.051107	5.349019
C	4.304604	0.302091	3.656509
H	5.026770	0.969898	4.132778
C	3.850539	0.586361	2.356948
H	4.224954	1.475965	1.849998
C	2.657618	1.861310	-0.295375

C	1.591481	2.782514	-0.306165
H	0.576691	2.389615	-0.185237
C	1.828412	4.154893	-0.489180
H	0.987957	4.852274	-0.497371
C	3.138824	4.625198	-0.674436
H	3.325853	5.691236	-0.823297
C	4.209775	3.714681	-0.679966
H	5.231373	4.070923	-0.833318
C	3.970834	2.343032	-0.492651
H	4.808854	1.643374	-0.512683
Cl	0.413349	-3.176877	0.127543
H	0.049586	-0.479826	1.258698
C	0.145685	0.261549	-2.393910
C	-0.133435	-1.116671	-2.474302
H	-0.634853	1.007076	-2.555898
H	1.155961	0.624876	-2.593623
H	-1.144988	-1.474168	-2.676799
H	0.659993	-1.843762	-2.648278

3. Burgess's catalyst

Acid E = -1592.90637528 Hartree

Ir	0.512424	-1.123172	-0.817026
C	1.567925	-0.783615	0.904308
N	1.595033	-1.575182	2.026770
C	2.466347	-1.057147	2.984991
C	2.999300	0.081001	2.460247
N	2.449142	0.240894	1.187882
N	-1.440893	-1.629574	0.257324
C	-2.678119	-1.216835	0.392343
O	-3.534413	-2.108732	0.964591
C	-2.827665	-3.367645	1.123283
C	-1.351433	-2.970532	0.931099
C	-0.582254	-2.907641	2.270424
C	0.955730	-2.895672	2.184778
H	2.627125	-1.546994	3.937450
H	3.719786	0.784137	2.856344
H	-3.198573	-4.056849	0.351976
H	-3.071150	-3.757377	2.118130
H	-0.842143	-3.665788	0.251645
H	-0.842380	-3.826389	2.821215
H	-0.942734	-2.062086	2.876216
H	1.366233	-3.302865	3.116795

H	1.301648	-3.538692	1.363009	H	-2.018438	0.893956	-1.421502
C	2.902325	1.287010	0.277975	H	-4.062984	-0.601972	-1.917871
C	2.336241	2.581345	0.390942	H	-5.166606	-1.045091	-0.597101
C	2.831715	3.576940	-0.474035	H	-6.140556	0.773025	-2.001237
C	3.848721	3.297173	-1.394343	H	-5.395688	2.184771	2.025805
C	4.404766	2.014174	-1.460891	H	-2.693739	3.261055	-1.180323
C	3.953572	0.976764	-0.622405	H	-4.613411	3.880026	0.330468
C	1.273591	2.930839	1.435736	H	-3.251070	3.240819	1.267898
C	4.646335	-0.387565	-0.652599	H	-5.044048	3.040575	-2.050448
C	4.889403	-0.909822	-2.087790	H	-3.987636	1.812268	-2.769545
C	5.986763	-0.322549	0.126532	H	-6.693599	0.722952	0.449091
C	1.923562	3.595071	2.678378	H	-6.653256	2.392762	-0.145174
C	0.167371	3.856066	0.876412	C	-0.552591	-1.075612	-2.808272
C	-3.399918	0.080556	0.062974	C	-0.188180	-2.396124	-2.526362
C	-4.082617	0.593406	1.380487	H	0.690805	-2.843391	-2.986571
C	-2.507387	1.214558	-0.489965	H	0.042497	-0.475321	-3.495421
C	-4.523613	-0.240188	-0.982348	H	-1.583745	-0.755851	-2.662105
C	-4.929655	1.853064	1.084547	H	-0.931936	-3.097794	-2.147891
C	-3.358647	2.479069	-0.780221	H	-0.040929	0.595398	-0.796215
C	-5.364542	1.027474	-1.262326	H	0.698930	0.607613	-1.198434
C	-6.027806	1.506733	0.050778	H	1.884646	-1.028863	-1.593991
C	-4.021754	2.970942	0.525699	H	0.941224	-2.635352	-0.543880
C	-4.450814	2.140118	-1.822947	Base E = -1592.48290523 Hartree			
H	2.421595	4.585489	-0.420422				
H	4.217437	4.084691	-2.052836	Ir	0.484824	-1.049270	-0.846459
H	5.211205	1.816837	-2.167302	C	1.552425	-0.802207	0.858384
H	3.997500	-1.115882	-0.145667	N	1.562069	-1.626109	1.972098
H	0.796152	1.994783	1.765801	C	2.442493	-1.160353	2.950784
H	5.837340	-0.007715	1.169789	C	3.009470	-0.022790	2.462026
H	6.469419	-1.311399	0.133711	N	2.466825	0.189892	1.192077
H	6.679031	0.390940	-0.345162	N	-1.482705	-1.616177	0.252286
H	3.960594	-0.922590	-2.675981	C	-2.722331	-1.245241	0.399633
H	5.627916	-0.298736	-2.627434	O	-3.586314	-2.197052	0.895182
H	5.283796	-1.935894	-2.046000	C	-2.841941	-3.439106	0.988972
H	1.155758	3.824881	3.432477	C	-1.373430	-2.996469	0.820264
H	2.676376	2.945541	3.146603	C	-0.596173	-3.002587	2.156090
H	2.419552	4.536225	2.397913	C	0.941112	-2.955811	2.047462
H	-0.257063	3.469112	-0.061052	H	2.581266	-1.678200	3.892196
H	-0.645365	3.952619	1.611296	H	3.741831	0.652685	2.884741
H	0.547064	4.869525	0.680398	H	-3.189473	-4.099791	0.181184
H	-4.717746	-0.198035	1.802181	H	-3.075563	-3.889930	1.962048
H	-3.302820	0.827159	2.125983	H	-0.843076	-3.616039	0.087209
H	-1.720411	1.456826	0.243250	H	-0.835447	-3.956965	2.656270

H	-0.964273	-2.197210	2.811630	H	-3.847303	0.487802	2.234984
H	1.374895	-3.429290	2.939040	H	-1.914490	1.405321	0.887187
H	1.265539	-3.515525	1.157889	H	-1.753997	1.081286	-0.830383
C	2.978179	1.231007	0.319252	H	-3.636491	-0.345674	-2.027984
C	2.464127	2.542260	0.443526	H	-4.981782	-0.973385	-1.051034
C	3.046427	3.548927	-0.350487	H	-5.686639	1.023553	-2.389912
C	4.093489	3.259026	-1.232868	H	-5.911570	1.841572	1.857998
C	4.582203	1.950960	-1.334081	H	-2.611558	3.392997	-0.474473
C	4.040916	0.907277	-0.559851	H	-4.845215	3.770570	0.632692
C	1.335096	2.882878	1.415110	H	-3.695499	3.015385	1.756366
C	4.637925	-0.498649	-0.644964	H	-4.690098	3.277836	-1.879717
C	4.835476	-0.975886	-2.102081	H	-3.449455	2.164597	-2.492716
C	5.978275	-0.565784	0.131907	H	-6.769820	0.620925	-0.158834
C	1.884197	3.569042	2.691740	H	-6.657867	2.361917	-0.490766
C	0.250648	3.766521	0.758536	C	-0.562329	-0.619894	-2.705511
C	-3.443250	0.062190	0.121465	C	-0.341100	-2.025451	-2.608749
C	-4.425091	0.366504	1.302443	H	0.441778	-2.499202	-3.200011
C	-2.492707	1.272060	-0.041781	H	0.058082	-0.015242	-3.366699
C	-4.298865	-0.117663	-1.178089	H	-1.564977	-0.221924	-2.544666
C	-5.233148	1.652668	1.009225	H	-1.174247	-2.684416	-2.350113
C	-3.310411	2.551719	-0.345165	H	0.303013	0.596868	-0.743437
C	-5.103814	1.171457	-1.465580	H	1.797257	-0.763145	-1.665349
C	-6.060467	1.457321	-0.284058	H	0.980175	-2.645250	-0.691415
C	-4.271218	2.848277	0.829200				
C	-4.127942	2.357476	-1.644573				
H	2.672537	4.571371	-0.279839				
H	4.529235	4.053039	-1.842176				
H	5.400425	1.736450	-2.022985				
H	3.933852	-1.196704	-0.173295				
H	0.856080	1.939234	1.712134				
H	5.848977	-0.283101	1.187389				
H	6.388189	-1.587804	0.099478				
H	6.723371	0.113922	-0.311179				
H	3.893271	-0.919293	-2.663628				
H	5.596408	-0.380778	-2.631088				
H	5.174998	-2.023112	-2.105386				
H	1.063432	3.788141	3.393183				
H	2.616018	2.933872	3.212347				
H	2.380984	4.519898	2.442160				
H	-0.109513	3.312297	-0.174024				
H	-0.603404	3.883315	1.443558				
H	0.627905	4.775734	0.530915				
H	-5.111436	-0.479679	1.450085				

4. Pfaltz' catalyst 1

Acid E = -1290.29206527 Hartree

Ir	0.282933	-1.542008	-0.530759
P	-1.243151	0.156501	-0.054440
N	1.781960	-0.272189	0.533166
O	2.668017	0.554079	2.436840
C	1.562448	0.274183	1.703684
C	3.790612	-0.083987	1.746036
C	3.270774	-0.251696	0.306003
C	0.289989	0.646405	2.359513
C	-0.981974	0.682231	1.714218
C	-2.104793	1.101030	2.450284
C	-2.000724	1.473328	3.800821
C	-0.755199	1.430167	4.437995
C	0.376513	1.025119	3.720428
H	3.984407	-1.038376	2.255705
H	4.651151	0.580147	1.860195

H	3.567027	-1.226284	-0.103557
C	3.765234	0.866272	-0.680487
C	3.517770	2.285809	-0.117962
C	3.058762	0.749390	-2.049975
C	5.284736	0.643837	-0.895369
C	-1.051928	1.695715	-1.068926
C	-0.753620	2.945959	-0.491168
C	-0.619857	4.083060	-1.306205
C	-0.784833	3.980293	-2.695545
C	-1.087182	2.735962	-3.275643
C	-1.217570	1.597474	-2.468606
C	-3.035209	-0.282862	-0.173762
C	-3.998725	0.671793	-0.564473
C	-5.355964	0.316597	-0.616172
C	-5.759011	-0.983872	-0.273806
C	-4.802154	-1.934948	0.118142
C	-3.443857	-1.590313	0.164700
H	3.855509	3.034405	-0.849925
H	2.448753	2.467554	0.067096
H	4.068621	2.473240	0.815591
H	3.528086	1.436781	-2.769675
H	1.997087	1.026270	-1.979140
H	3.141026	-0.267359	-2.466894
H	5.676986	1.401243	-1.589413
H	5.860966	0.729981	0.038363
H	5.489298	-0.347003	-1.330976
H	-1.464676	0.638223	-2.928457
H	-0.633567	3.041253	0.588687
H	-0.391339	5.047210	-0.850598
H	-0.683699	4.865053	-3.324780
H	-1.225476	2.652183	-4.354122
H	-2.702198	-2.335060	0.453809
H	-3.695770	1.683787	-0.835465
H	-6.094523	1.056658	-0.926133
H	-6.813782	-1.257169	-0.317453
H	-5.110632	-2.947717	0.379436
H	-3.082429	1.122045	1.969357
H	-2.892655	1.784535	4.345069
H	-0.658420	1.707481	5.487571
H	1.345756	0.996294	4.213285
C	1.759789	-3.091496	-1.284147
C	1.418435	-3.395874	0.038465
H	2.085236	-3.133856	0.860418

H	0.691225	-4.175615	0.255221
H	1.286353	-3.622917	-2.108477
H	2.703705	-2.599599	-1.518052
H	-0.836436	-2.528306	-1.079650
H	-0.204201	-2.009726	0.918692
H	0.871859	-0.723457	-2.028911
H	0.225554	-1.209565	-2.276898

Base E = -1289.87970964 Hartree

Ir	0.339604	-1.627646	-0.325244
P	-1.195074	0.069255	-0.101580
N	1.786765	-0.181239	0.598978
O	2.639919	1.006049	2.335730
C	1.540029	0.553754	1.649495
C	3.773805	0.281138	1.773065
C	3.271547	-0.148240	0.381237
C	0.250952	0.960911	2.243032
C	-1.017743	0.826906	1.602726
C	-2.166897	1.254306	2.294758
C	-2.094462	1.803052	3.584816
C	-0.848077	1.942453	4.208700
C	0.308502	1.527310	3.539613
H	3.981943	-0.573187	2.434578
H	4.623888	0.970027	1.773660
H	3.600358	-1.166999	0.139913
C	3.735177	0.809732	-0.776805
C	3.364167	2.282404	-0.482257
C	3.106729	0.398850	-2.125881
C	5.275255	0.674623	-0.902370
C	-1.078448	1.556819	-1.229507
C	-1.186154	2.881144	-0.757913
C	-1.110675	3.962901	-1.652419
C	-0.937600	3.731713	-3.025534
C	-0.833374	2.413545	-3.502044
C	-0.894863	1.332850	-2.610048
C	-3.003451	-0.374387	-0.190431
C	-3.982309	0.509907	-0.688560
C	-5.331506	0.120675	-0.731483
C	-5.713901	-1.150259	-0.273867
C	-4.741227	-2.035800	0.220021
C	-3.391506	-1.654820	0.256782
H	3.699698	2.920572	-1.314457
H	2.275909	2.408271	-0.387846

H	3.837624	2.662334	0.436160	H	-3.411143	1.560157	1.876288
H	3.482231	1.063571	-2.920826	H	-4.062599	3.954932	2.029446
H	2.012731	0.462129	-2.099269	H	-3.042346	5.633802	0.486652
H	3.372506	-0.633999	-2.396785	H	-1.361087	4.908034	-1.211384
H	5.632359	1.284320	-1.746379	H	-0.685717	2.516510	-1.354845
H	5.810317	1.018074	-0.002960	C	-3.153539	-0.733915	-0.274861
H	5.569760	-0.369295	-1.096976	C	-3.557352	-1.927543	0.357499
H	-0.780310	0.310769	-2.975218	C	-4.741744	-2.564462	-0.044338
H	-1.324060	3.075768	0.306543	C	-5.520590	-2.022280	-1.078953
H	-1.185043	4.983278	-1.272095	C	-5.117389	-0.834862	-1.711849
H	-0.878328	4.571867	-3.719503	C	-3.938253	-0.188744	-1.312937
H	-0.693432	2.225600	-4.567966	H	-2.964617	-2.342452	1.171800
H	-2.627321	-2.345333	0.615858	H	-5.057076	-3.480505	0.456650
H	-3.695413	1.497653	-1.052037	H	-6.440639	-2.519462	-1.387820
H	-6.079711	0.810426	-1.126121	H	-5.722691	-0.406058	-2.511066
H	-6.762110	-1.452032	-0.310064	H	-3.638989	0.738830	-1.803858
H	-5.030624	-3.028981	0.567601	O	-1.468809	-0.450629	1.766209
H	-3.142210	1.144053	1.820858	C	-0.250834	-0.473551	2.598674
H	-3.008621	2.113553	4.093206	C	0.283475	0.947722	2.821548
H	-0.771719	2.364300	5.211630	H	-0.480846	1.563247	3.313412
H	1.278491	1.627700	4.021990	C	-0.768888	-1.095740	3.908592
C	1.839751	-3.019417	-1.054977	H	-1.074105	-2.141447	3.759191
C	1.537330	-3.319986	0.309695	H	0.559703	1.429658	1.874026
H	2.237410	-3.033839	1.098417	H	1.173902	0.927462	3.468315
H	0.913464	-4.178012	0.555415	H	-0.011465	-1.055779	4.703115
H	1.433746	-3.642158	-1.850958	H	-1.644012	-0.527753	4.249528
H	2.780188	-2.529099	-1.310082	N	1.460072	-0.807355	0.743339
H	-0.260292	-1.959067	1.200496	O	3.127211	-1.077123	2.245629
H	0.520843	-1.145307	-1.903317	C	2.712635	-0.586465	1.053589
H	-0.700723	-2.679265	-0.893715	C	2.001432	-1.801506	2.832160
				C	0.798392	-1.424012	1.931734
				H	0.256985	-2.322768	1.604891
				H	2.242594	-2.871350	2.795022
				H	1.928327	-1.475788	3.873658
				C	3.753217	0.146297	0.309856
				C	5.073620	-0.356946	0.299154
				C	6.086435	0.354093	-0.356236
				C	5.799108	1.584197	-0.971745
				C	4.493853	2.103354	-0.933594
				C	3.469152	1.386091	-0.301479
				H	7.100632	-0.044855	-0.376063
				H	4.275945	3.070334	-1.387917
				H	5.297959	-1.299707	0.797639

5. Pfaltz' catalyst 2

Acid E = -1326.21435527 Hartree

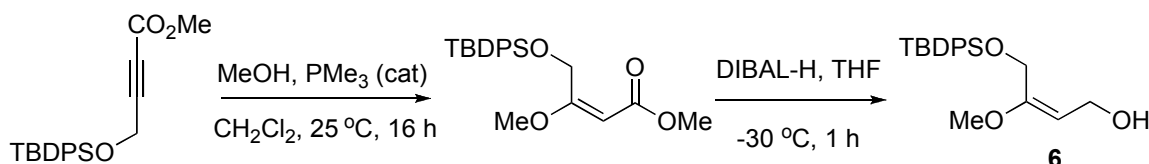
Ir	0.247694	-0.573338	-1.107004
P	-1.566921	0.093006	0.168098
C	-1.989931	1.883478	0.259956
C	-2.953540	2.292564	1.209694
C	-3.322438	3.641581	1.292446
C	-2.747758	4.585781	0.423050
C	-1.801506	4.179428	-0.529918
C	-1.417597	2.830948	-0.610455

H	6.592589	2.142807	-1.468976	O	-1.435427	-0.025009	1.796363
H	2.459401	1.792113	-0.254942	C	-0.191270	0.063503	2.563846
H	-0.628500	-2.105816	-1.447315	C	0.385252	1.487385	2.501540
H	-0.175481	-2.323285	-0.775353	H	-0.344317	2.205375	2.900506
H	0.657681	0.960777	-1.154122	C	-0.675298	-0.279579	3.988519
H	-0.648923	-0.266796	-2.389743	H	-0.990022	-1.331634	4.054824
C	1.845450	-0.401477	-2.758485	H	0.626167	1.773128	1.468923
C	1.886383	-1.699400	-2.260415	H	1.306189	1.559116	3.101612
H	2.643550	-1.989895	-1.531891	H	0.099684	-0.089321	4.744331
H	1.395601	-2.510805	-2.797282	H	-1.542406	0.351089	4.225708
H	1.307987	-0.174779	-3.676895	N	1.500565	-0.640588	0.796849
H	2.570251	0.338327	-2.426541	O	3.155848	-0.603448	2.353589

Base E = -1325.80867529 Hartree

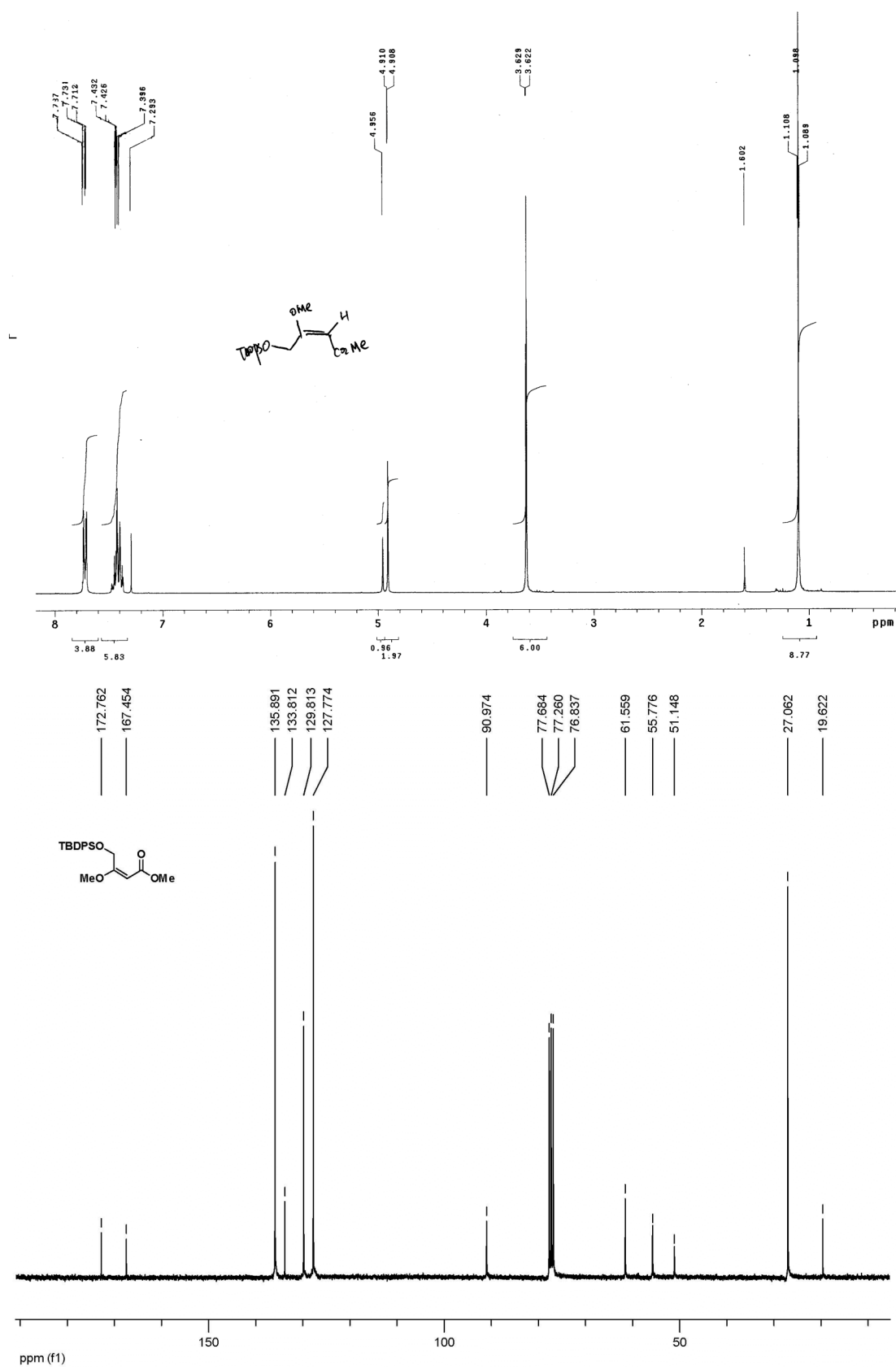
Ir	0.194158	-0.898190	-1.007966	C	2.743724	-0.354048	1.069480
P	-1.517096	0.128238	0.086752	C	2.036350	-1.245953	3.029001
C	-1.887255	1.941943	-0.120712	C	0.836012	-1.018732	2.078972
C	-2.768621	2.583720	0.777392	H	0.277562	-1.947067	1.909609
C	-3.052275	3.949188	0.632733	H	2.282647	-2.311279	3.142590
C	-2.467597	4.683832	-0.414460	H	1.954425	-0.781431	4.016261
C	-1.598016	4.048087	-1.314098	C	3.786691	0.252096	0.223489
C	-1.304359	2.681509	-1.165857	C	5.146941	0.060158	0.558191
H	-3.227054	2.013671	1.586919	C	6.150817	0.668057	-0.206325
H	-3.730977	4.439447	1.333068	C	5.809088	1.485743	-1.296754
H	-2.691066	5.746278	-0.526600	C	4.457293	1.690980	-1.620833
H	-1.143193	4.613807	-2.129165	C	3.446878	1.077341	-0.869311
H	-0.618269	2.177810	-1.849603	H	7.198610	0.506095	0.050601
C	-3.199667	-0.631385	-0.096800	H	4.186661	2.328362	-2.463847
C	-3.479930	-1.858866	0.536036	H	5.407984	-0.565391	1.410812
C	-4.722755	-2.480922	0.353054	H	6.592376	1.960961	-1.889533
C	-5.692040	-1.893694	-0.478365	H	2.395436	1.211592	-1.125499
C	-5.413038	-0.678613	-1.122031	H	-0.759123	-1.172884	-2.243993
C	-4.173464	-0.046262	-0.929098	H	-0.533045	-2.174311	-0.210158
H	-2.721653	-2.323896	1.165720	H	0.598422	0.541512	-1.738930
H	-4.932069	-3.428019	0.853564	C	1.808892	-1.523637	-2.357527
H	-6.656486	-2.382928	-0.625360	C	1.317664	-2.657585	-1.652064
H	-6.158247	-0.217289	-1.772267	H	1.894125	-3.065706	-0.819986
H	-3.968924	0.900835	-1.430117	H	0.655605	-3.368751	-2.143365
				H	1.512479	-1.357432	-3.392111
				H	2.767370	-1.088514	-2.078112

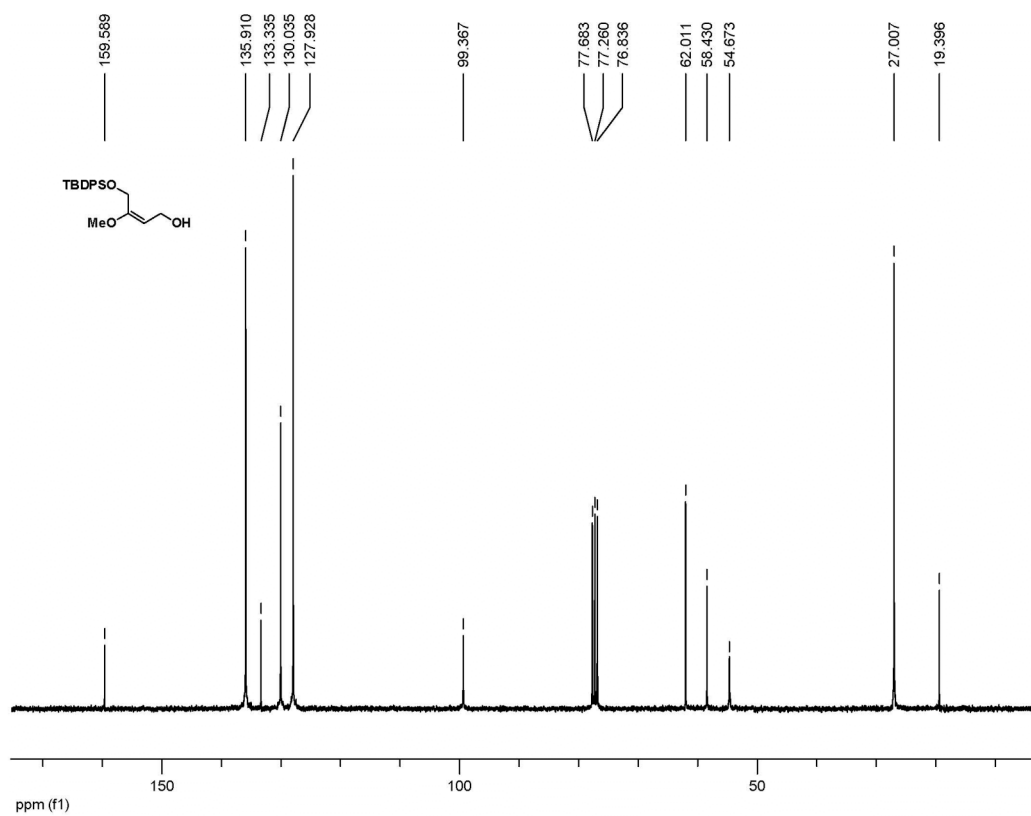
Synthesis of Alkene 6. According to the method of Paintner and co-workers,²⁸ methanol was added to methyl butynoate, using trimethylphosphine as a nucleophilic catalyst to give corresponding vinyl ether esters. Then ester was reduced by DIBAL to give the vinyl ether alcohol **6**.



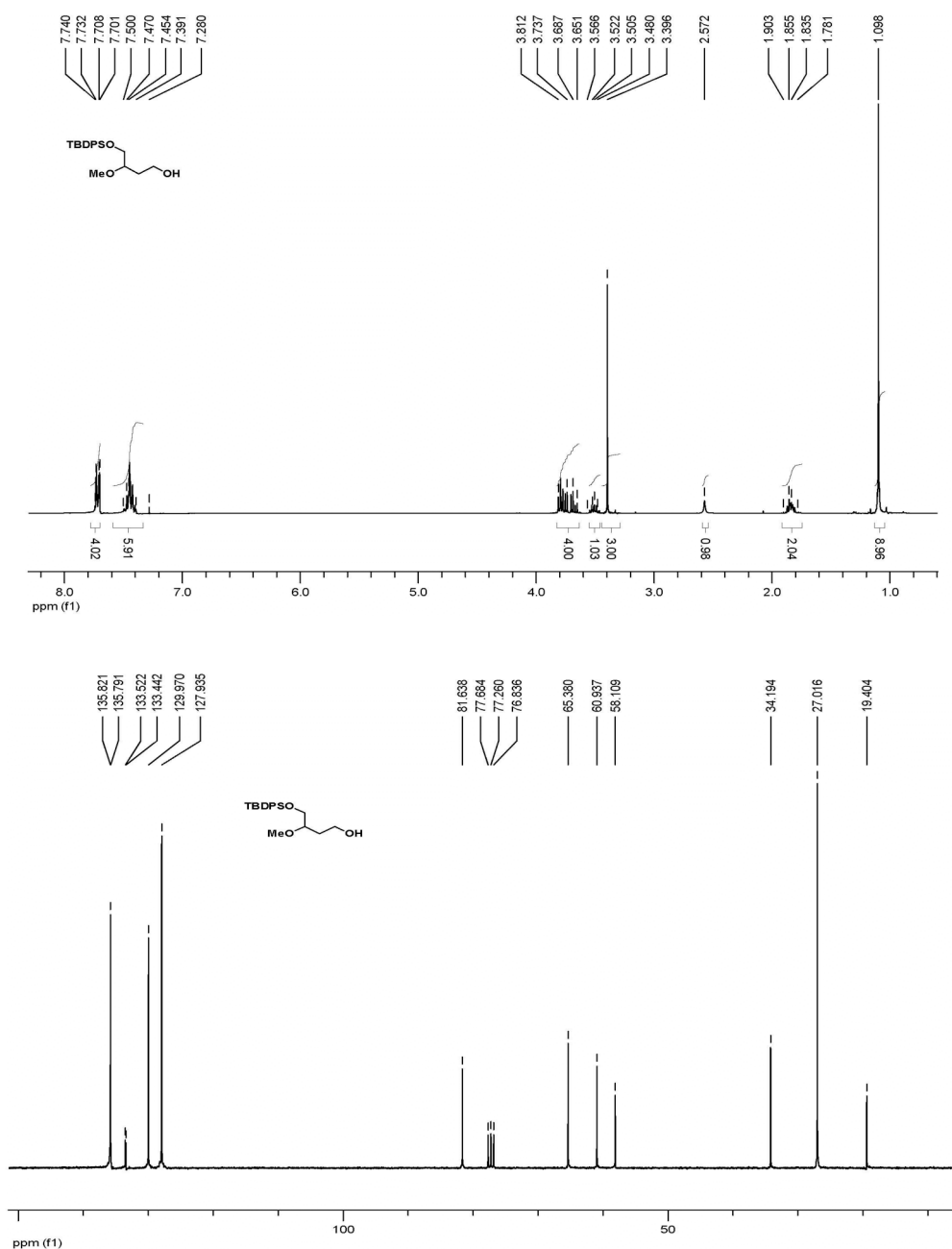
Methyl butynoate (5.0 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of methanol (15 mmol) and PMe_3 (0.5 mL, 1.0 M in THF, 0.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C by means of a syringe. Then the reaction mixture was allowed to warm to r.t. and stirred overnight. The solution was concentrated under reduced pressure. The crude product was purified by flash chromatography. ^1H NMR (300 MHz, CDCl_3) 7.74-7.70 (4H, m), 7.43-7.40 (6H, m), 4.96 (1H, s), 4.91 (2H, s), 3.63(3H, s), 3.62 (3H, s), 1.10 (9H, s); ^{13}C NMR (75 MHz, CDCl_3) 172.8, 167.5, 135.9, 133.8, 129.8, 127.8, 91.0, 61.6, 55.8, 51.1, 27.1, 19.6. MS (ESI): Exact mass calcd for $\text{C}_{22}\text{H}_{29}\text{O}_4\text{Si}[\text{M}+\text{H}]^+$ 385.2; Found 385.2.

To a cooled solution (-30 °C) of ester (0.89 g, 2.3 mmol) in THF (10 mL) was added DIBAL-H (1.0 M in Hexanes, 6.9 mL, 6.9 mmol) slowly via a syringe pump. The reaction mixture was stirred at -30 °C for 1 h, then the reaction was quenched with MeOH (5 mL). Et_2O (20 mL) was added and saturated solution of potassium sodium tartrate in water (20 mL) was then added. The resulting mixture was vigorously stirred for 1 h and the layers were separated. The aqueous layer was extracted with Et_2O (3×20 mL). The combined organic extracts were dried by K_2CO_3 and concentrated *in vacuo*. Purification by flash chromatography on basic Al_2O_3 eluting with EtOAc/Hexanes (20:80) gave the desired product **6** (0.46 g, 76%) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) 7.74-7.70 (4H, m), 7.49-7.39 (6H, m), 4.85 (1H, t, $J = 7.8$ Hz), 4.26 (2H, s), 4.10-4.05 (2H, m), 3.53 (3H, s), 1.49 (1H, t, $J = 5.7$ Hz), 1.07 (9H, s); ^{13}C NMR (75 MHz, CDCl_3) 159.6, 135.9, 133.3, 130.0, 127.9, 99.4, 62.0, 58.4, 54.7, 27.0, 19.4. MS (ESI): calcd for $\text{C}_{21}\text{H}_{28}\text{KO}_3\text{Si}[\text{M}+\text{K}]^+$ 395.1; Found 395.1.

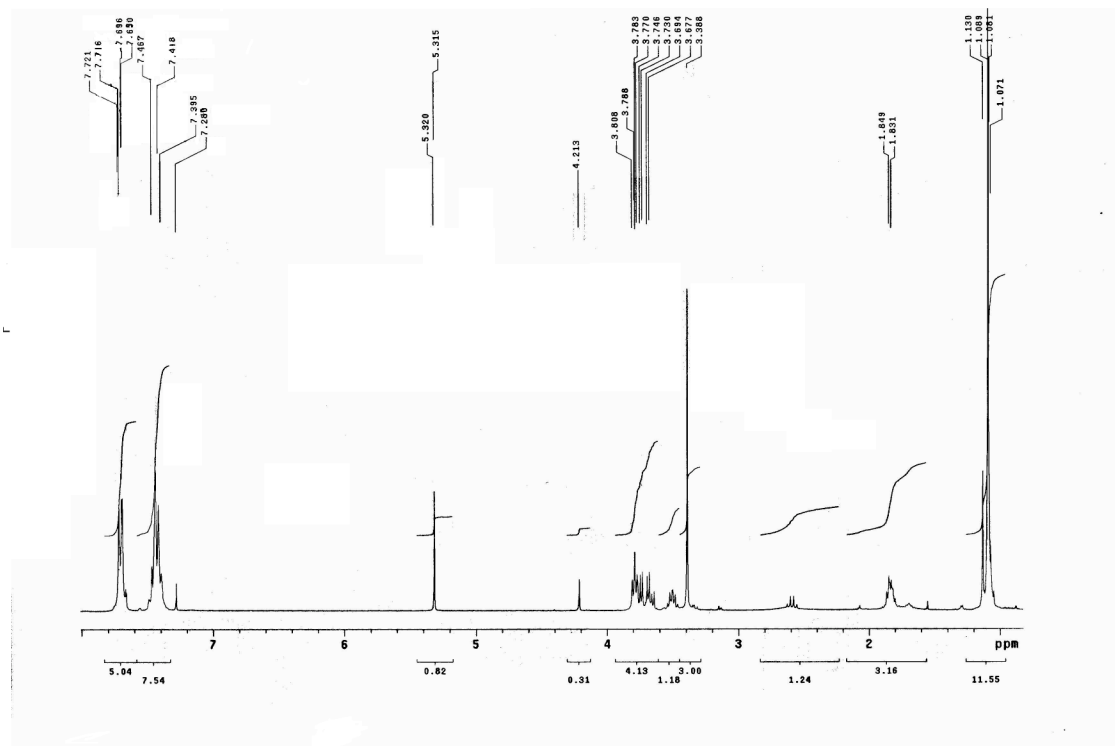
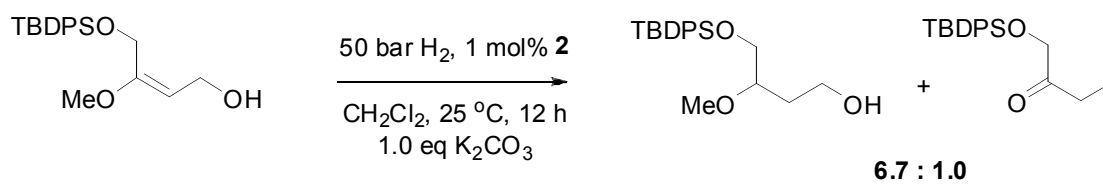


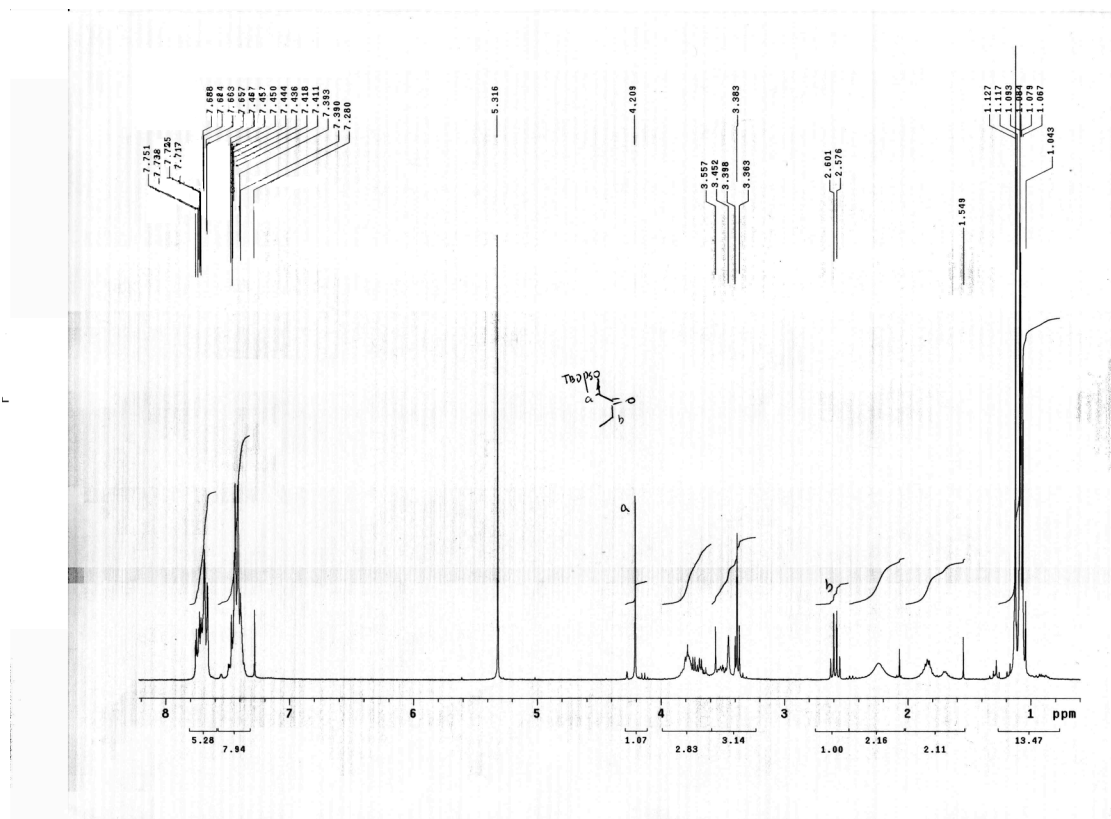
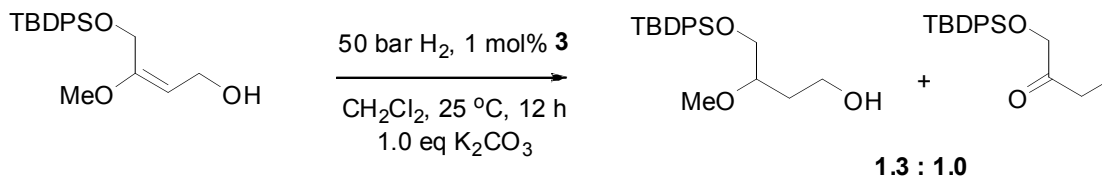


General Catalytic Hydrogenation Conditions. The corresponding alkenes were dissolved in CH_2Cl_2 (0.5 M) and the Iridium catalyst (1 mol %) was then added. The resulting solution was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was flushed with hydrogen for 1 min without stirring. The mixture was then stirred at 700 rpm under 50 bar H_2 . After 12 h, the bomb was vented and the solvent evaporated. The crude product was directly dissolved in 0.5 mL CDCl_3 and ^1H NMR was taken.

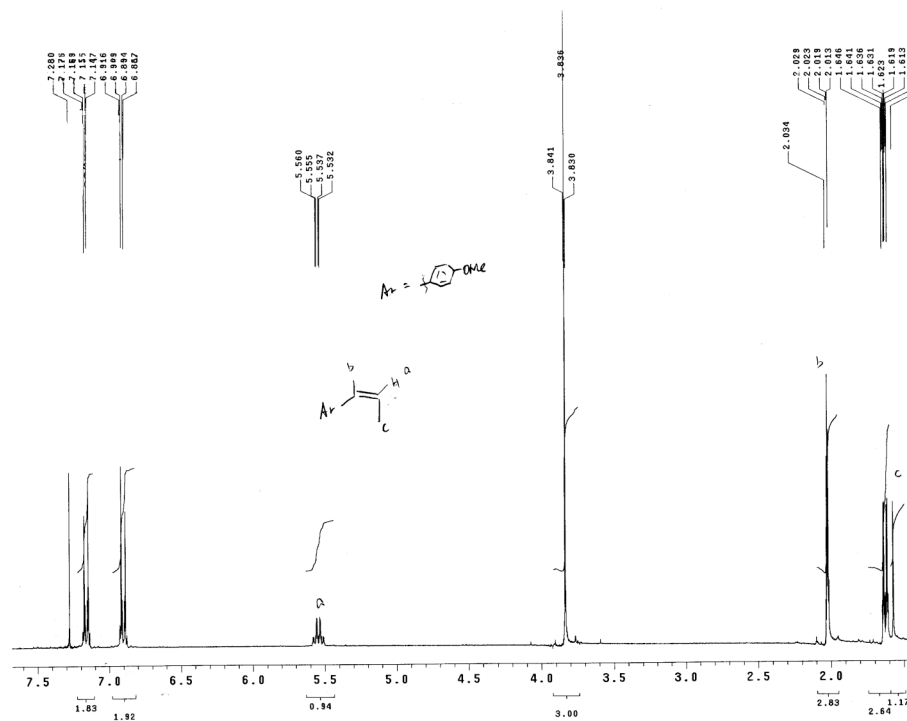
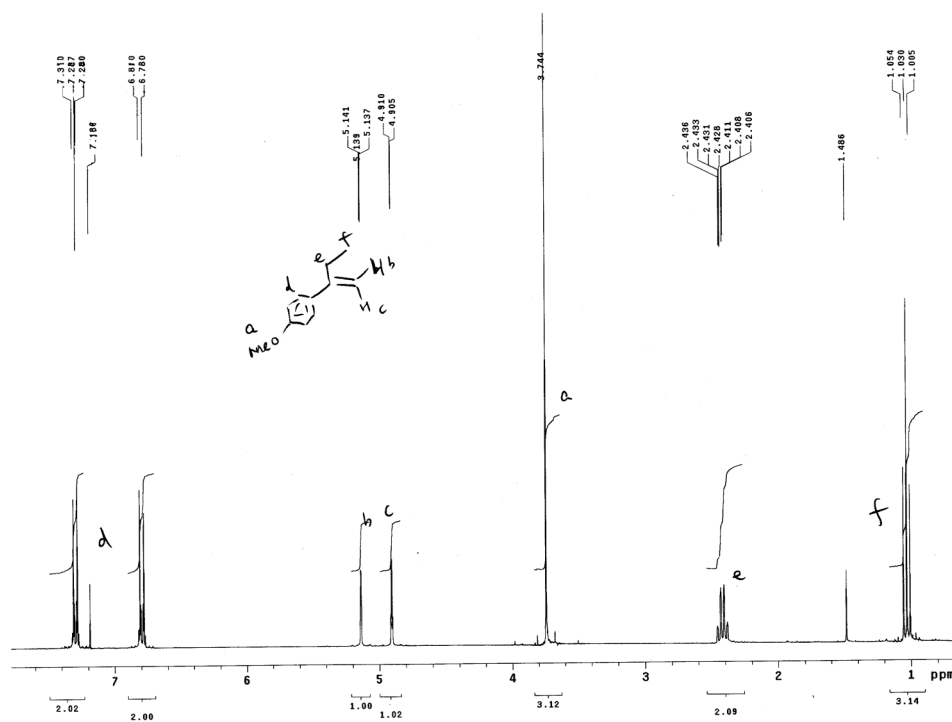




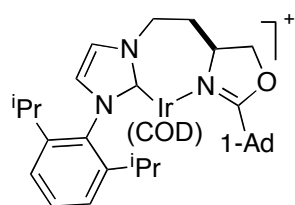
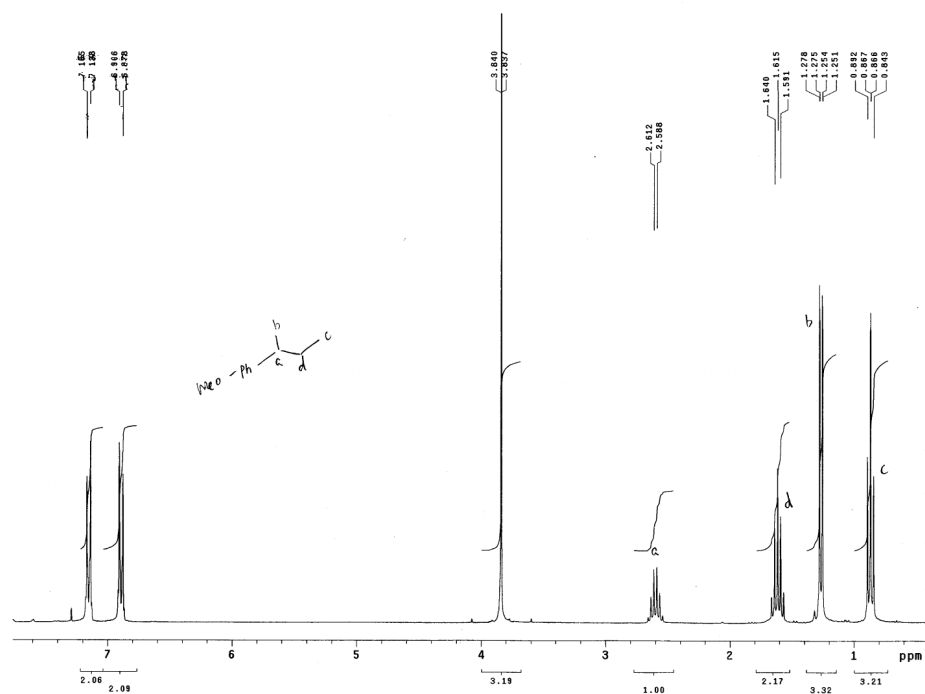
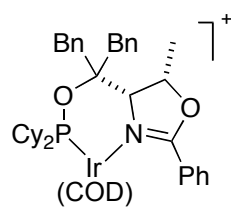
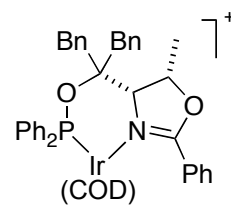




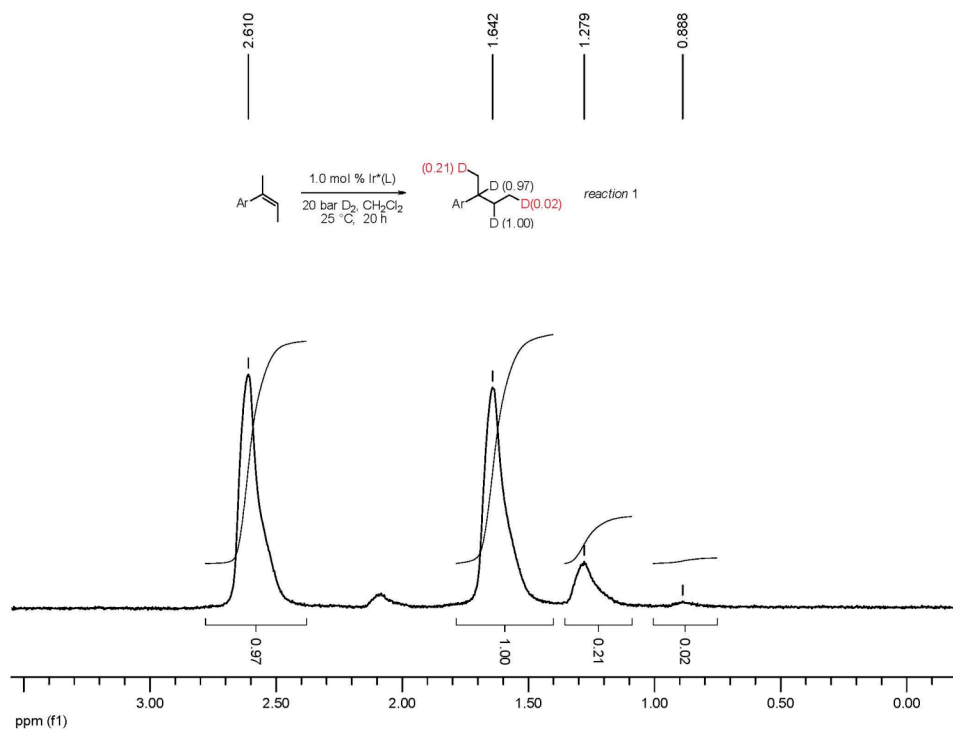
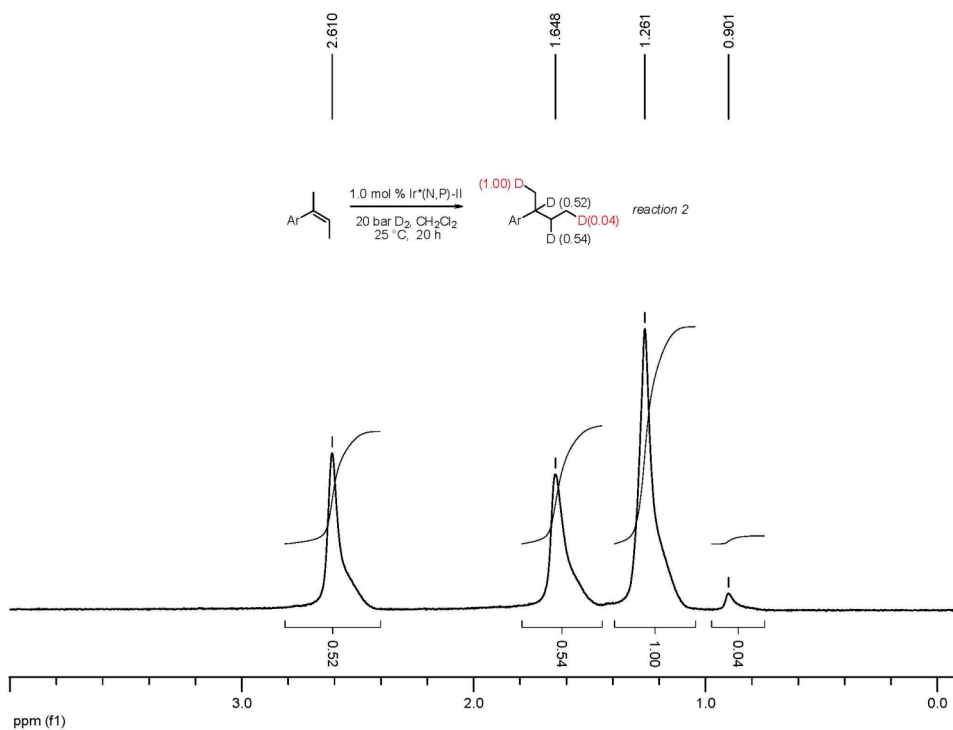
General Procedure for Deuteration: Alkene substrate (0.1 mmol), and the desired amount of iridium complex were added to a test tube containing a small stir bar and sealed with a rubber septum. Then, dry CH_2Cl_2 (0.2 mL) was added. The resulting solution was degassed by three cycles of freeze-pump-thaw and then the septum was removed and the tube was quickly placed in a bomb. The bomb was flushed with deuterium gas, and then pressurized with the desired amount of deuterium. The mixture was stirred at 700 rpm/s for 20 h. Upon completion, the bomb was vented, and the reaction mixture was placed in an NMR tube along with an additional 0.5 mL $CHCl_3$ and 1 drop of $CDCl_3$. 2H NMR was then taken.

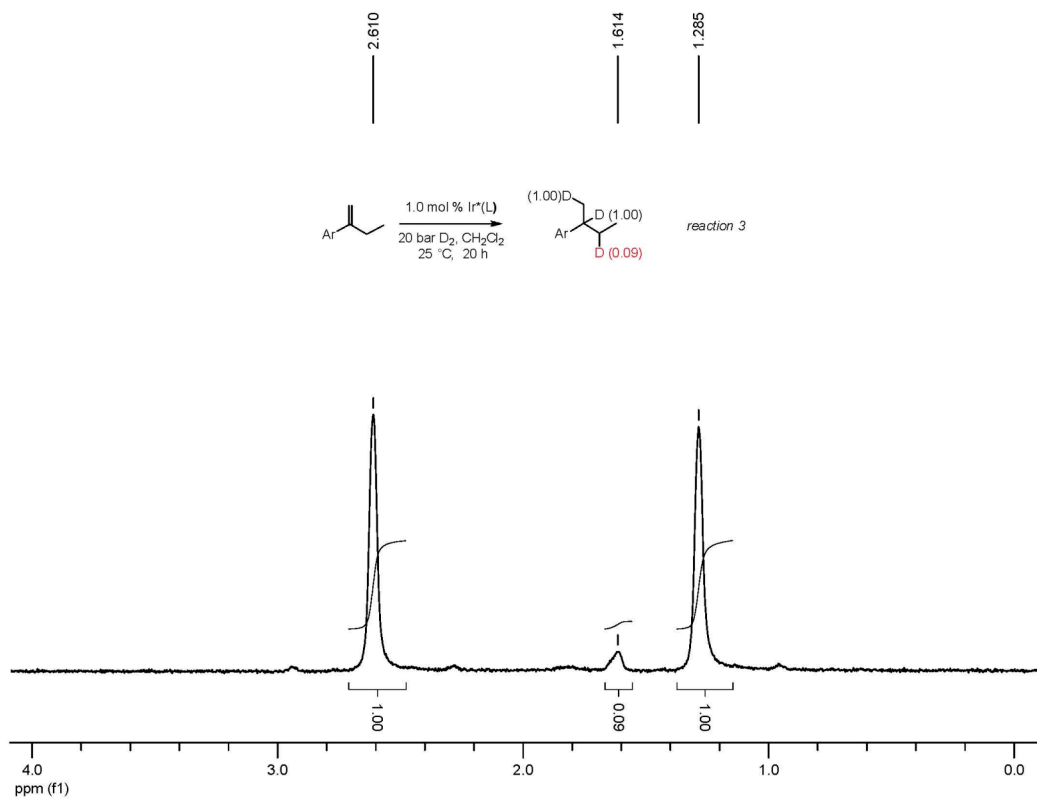
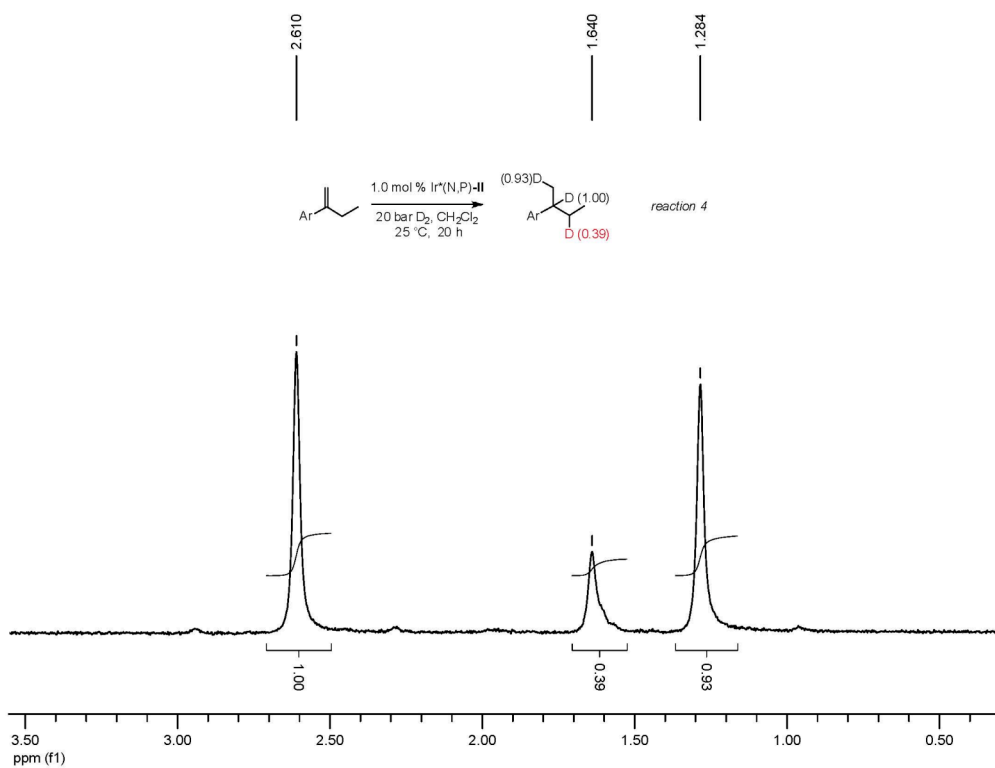
The ^1H NMR of Substrate **9**The ^1H NMR of Substrate **10**

The ^1H NMR of Hydrogenation Product of **9** and **10**

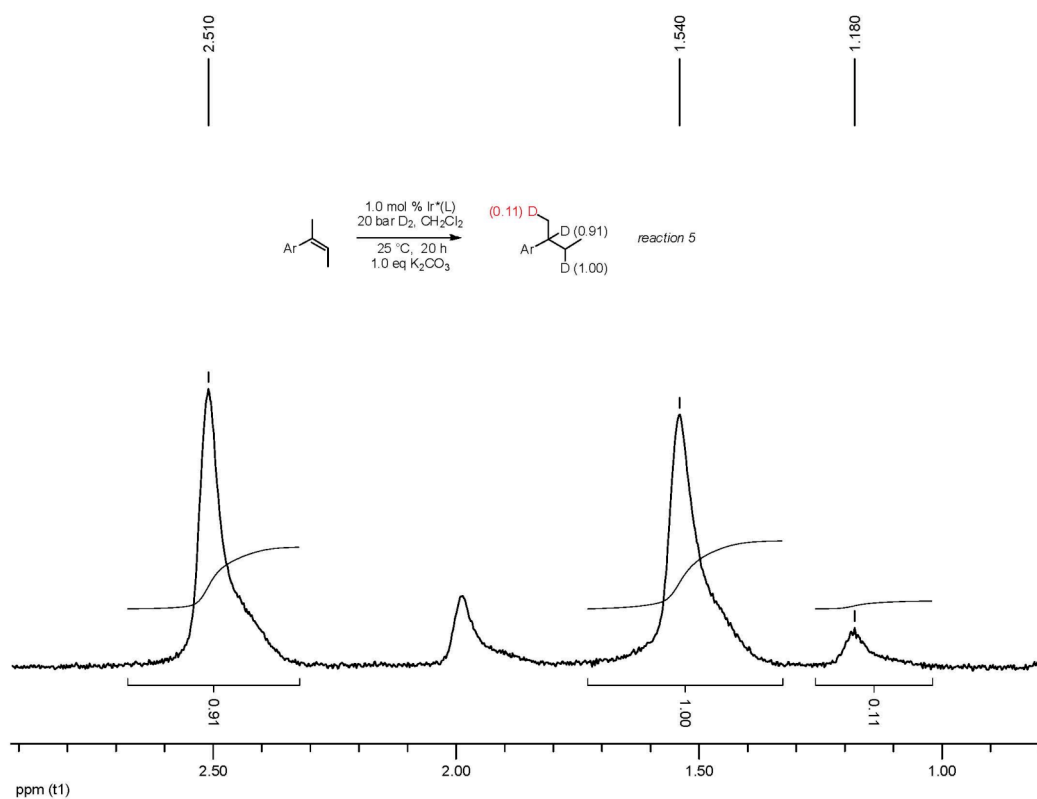
BARF⁻**Ir* (L)**BARF⁻**Ir* (N,P-I)**BARF⁻**Ir* (N,P-II)**

The catalysts used for deuteration reactions

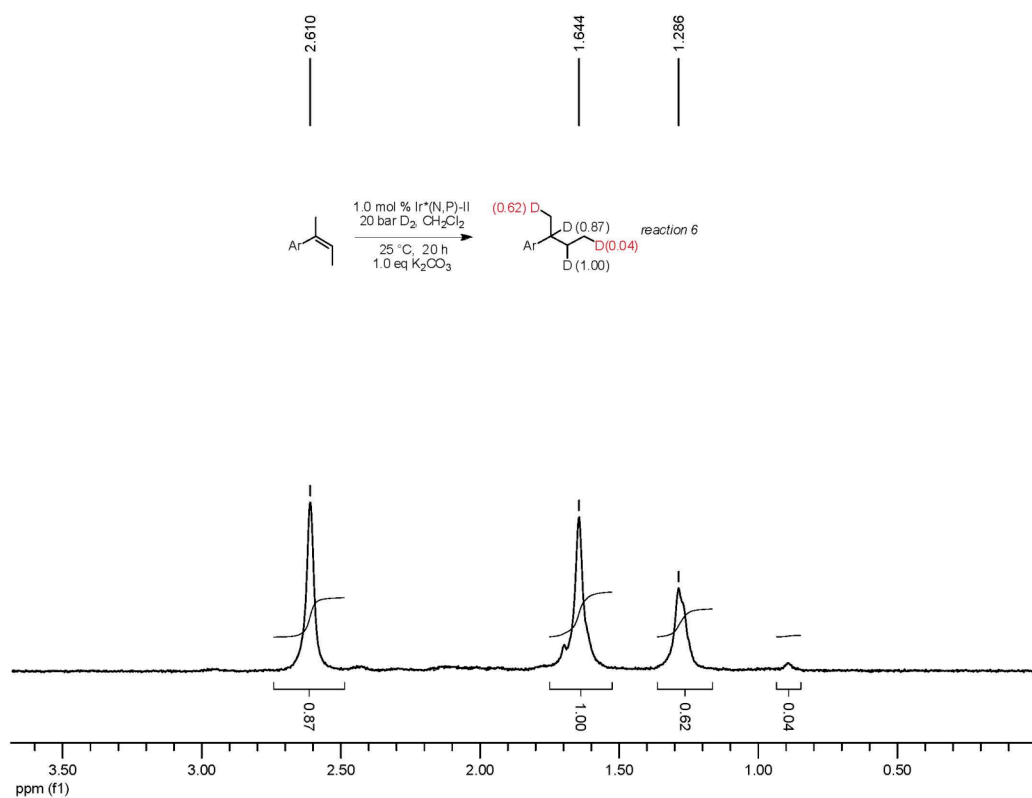
The ^2H NMR of Deuteration Product of Substrate **9** (entry 1)The ^2H NMR of Deuteration Product of Substrate **9** (entry 4)

The ^2H NMR of Deuteration Product of Substrate **10** (entry 1)The ^2H NMR of Deuteration Product of Substrate **10** (entry 4)

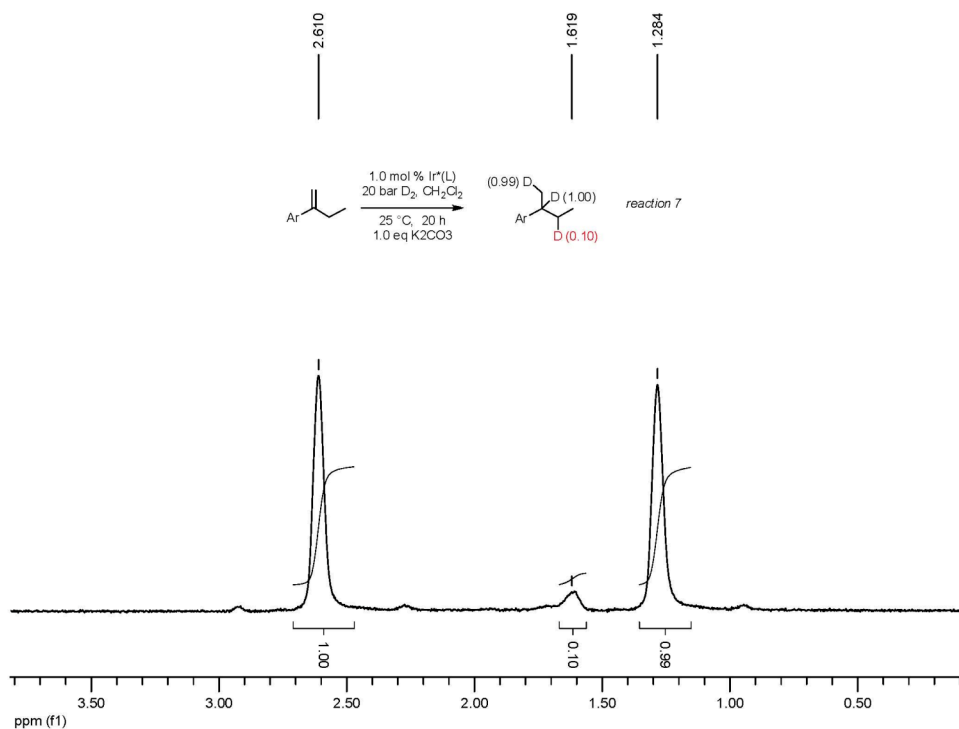
The ^2H NMR of Deuteration Product of Substrate **9** (entry 2, w/ K_2CO_3)



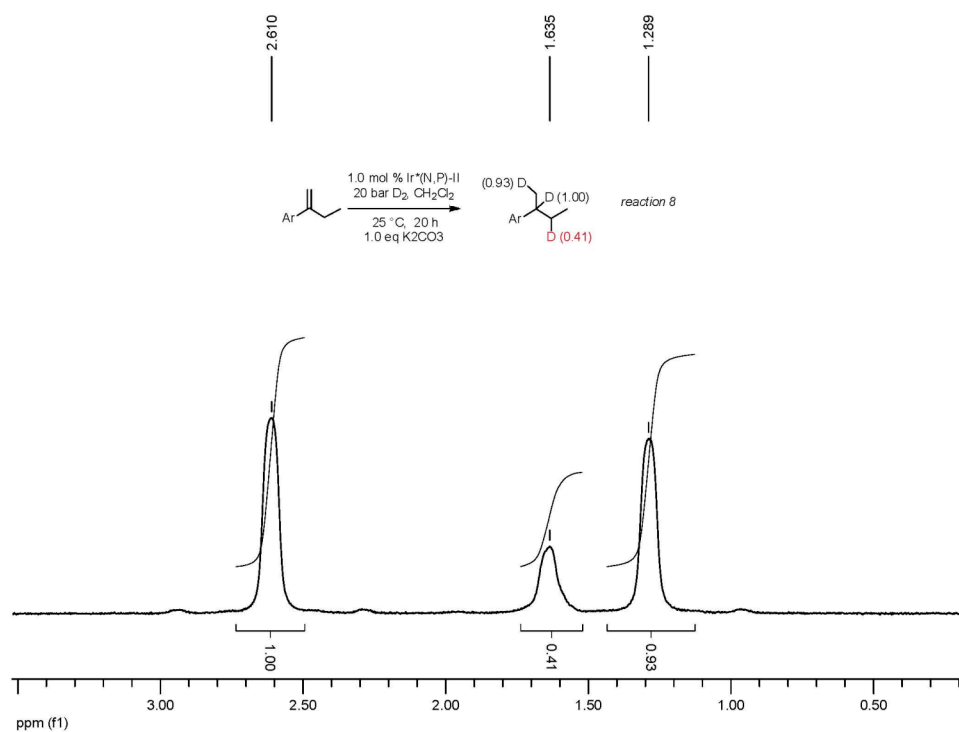
The ^2H NMR of Deuteration Product of Substrate **9** (entry 5, w/ K_2CO_3)



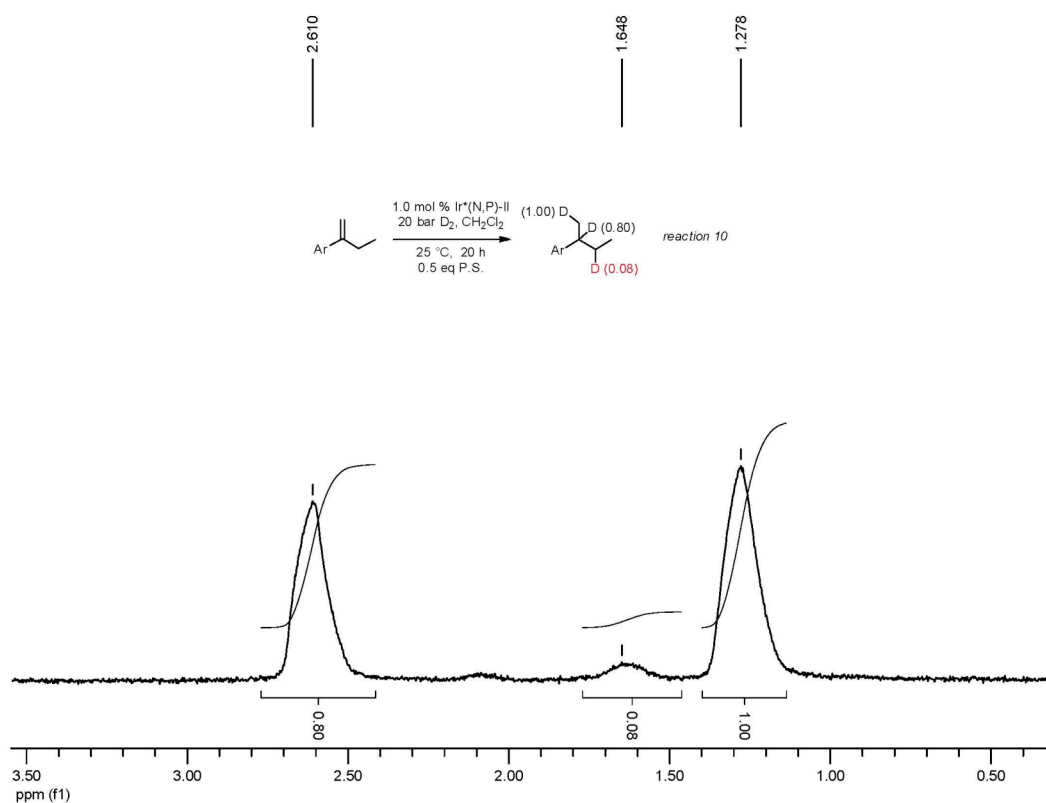
The ^2H NMR of Deuteration Product of Substrate **10** (entry 2, using catalyst $\text{Ir}^*(\text{L})$, w/
 K_2CO_3)



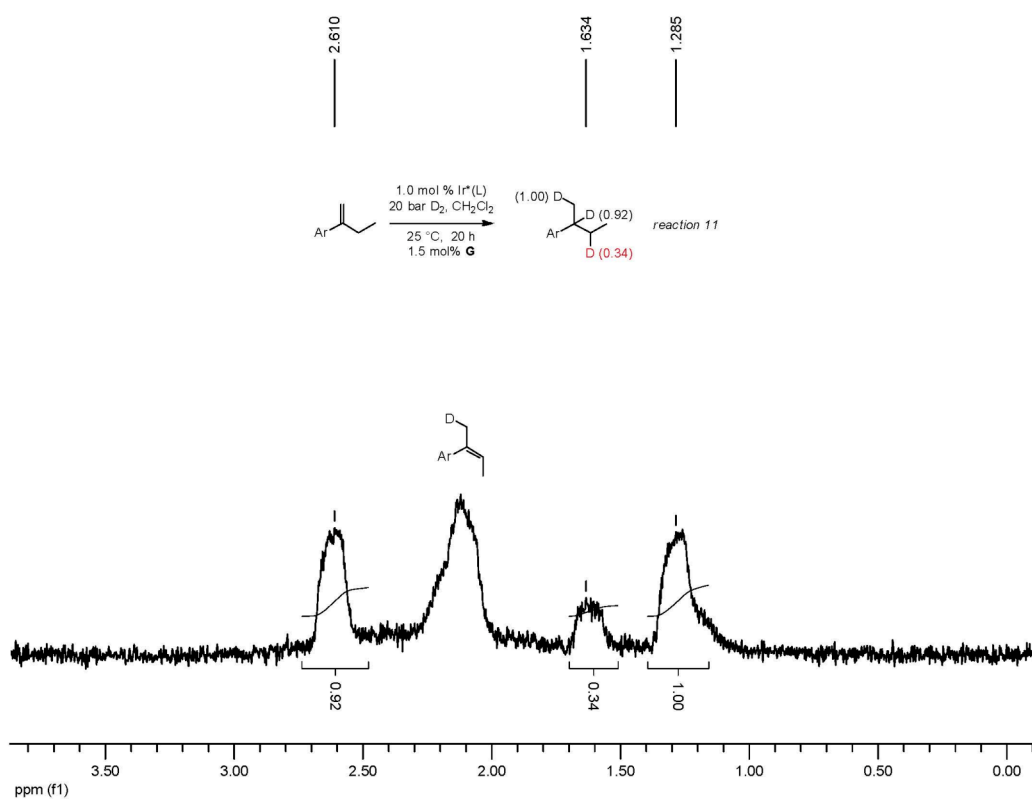
The ^2H NMR of Deuteration Product of Substrate **10** (entry 5, using catalyst $\text{Ir}^*(\text{N},\text{P-II})$
w/ K_2CO_3)



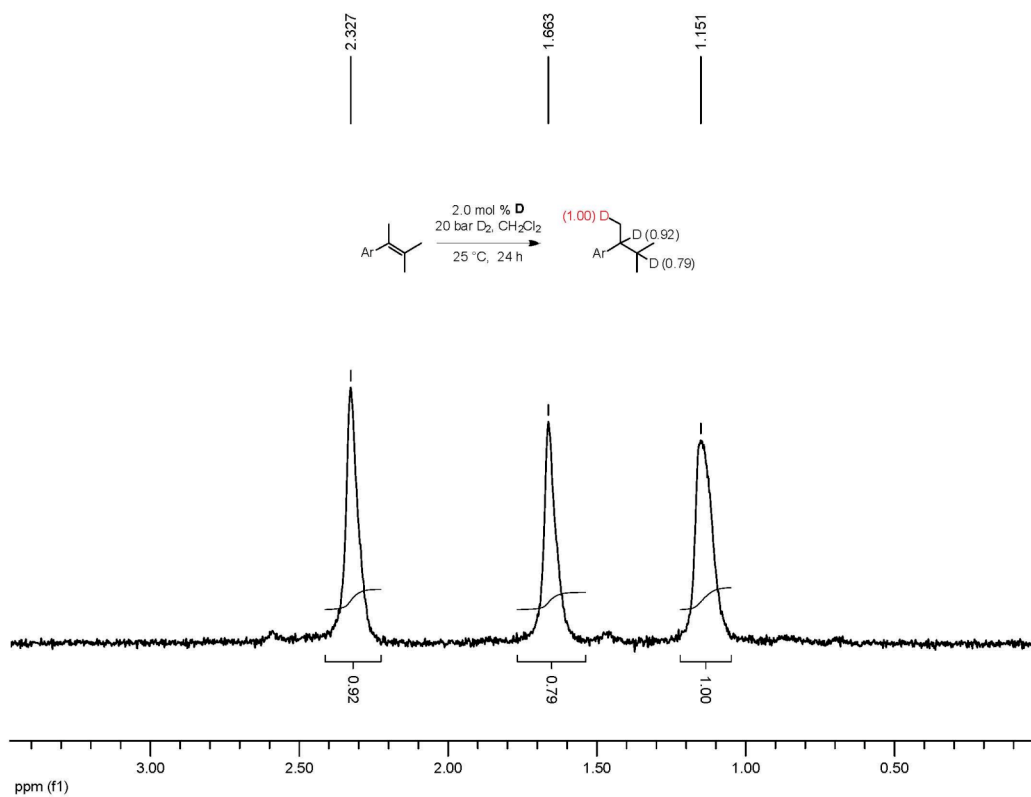
The ^2H NMR of Deuteration Product of Substrate **10** (entry 6, w/0.5 eq **11**)



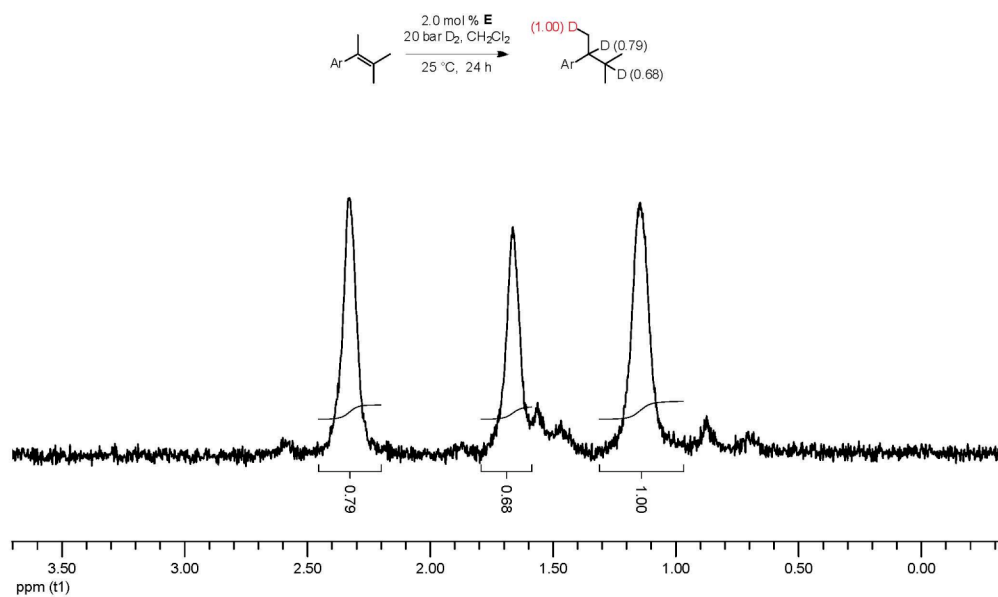
The ^2H NMR of Deuteration Product of Substrate **10** (entry 3, w/ 0.015 eq **12**)



The ^2H NMR of Deuteration Product of Substrate **14** (with catalyst Ir* (N,P-I))



The ^2H NMR of Deuteration Product of Substrate **14** (with catalyst Ir* (N,P-II))



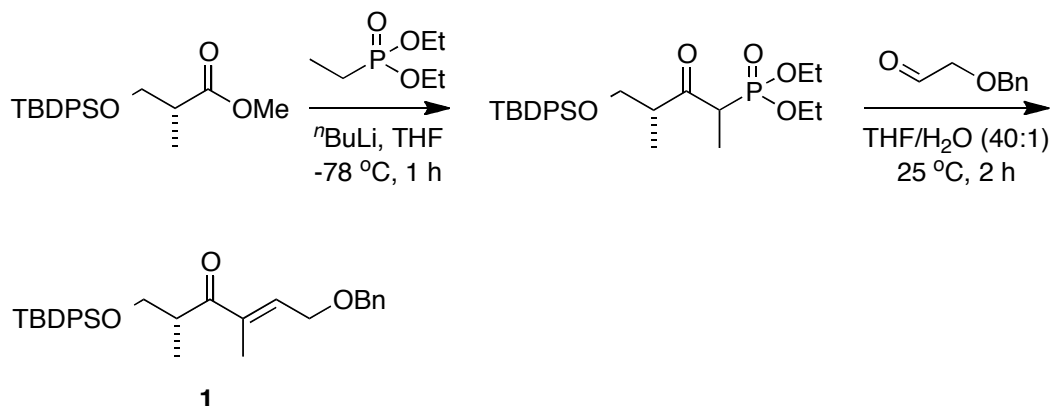
Reference:

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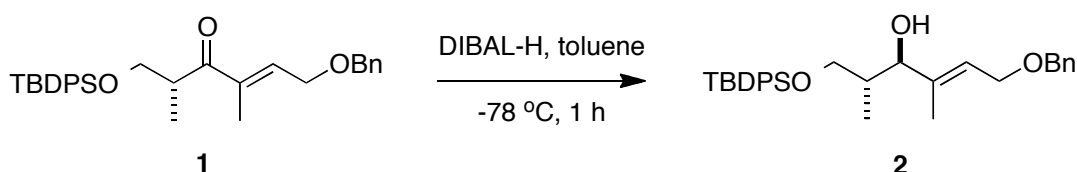
APPENDIX E

EXPERIMENTAL DATA FOR CHAPTER VI

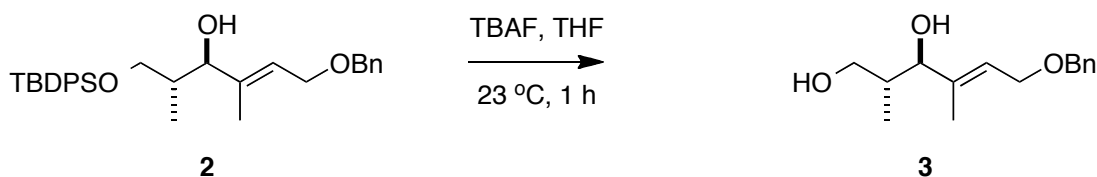


n BuLi (2.5M in Hexanes, 12.5 mL) was added to a solution of diethyl ethylphosphonate (5.66 g, 34.1mmol) in THF (70 mL) at -78 °C over 10 min. The resulting mixture was stirred at -78 °C for 0.5 h. Then a solution of 3-(*tert*-butyldiphenylsilyloxy)-2-(*R*)-methylpropionic acid methyl ester (4.86 g, 13.6 mmol) in THF (70 mL) was added to this mixture over 30 min. The solution was continued to stir for 0.5 h at -78 °C and then $\text{NH}_4\text{Cl(s)}$ (50 mL) was added to quench the reaction. The mixture was warmed to r.t. and diluted with H_2O (20 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried with Na_2SO_4 , and concentrated *in vacuo*. Purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (30:70) gave the desired phosphonate as a colorless oil (6.41 g, 13.1 mmol, 96%). ^1H NMR indicated the product as a mixture of two diastereoisomers. The purified phosphonate (7.30 g, 14.9 mmol) was dissolved in THF (80 mL) and H_2O (2 mL). The solution was cooled to 0 °C and Ba(OH)_2 (2.55 g, 14.9 mmol) was added in one portion. The mixture was stirred for 0.5 h and then a solution of benzyloxyacetaldehyde (2.3 mL, 16.4 mmol) in THF (10 mL) was added dropwise. The resulting mixture was continued to stir for 2 h at 25 °C before quenched with $\text{NaHCO}_3\text{(s)}$ (50 mL). The mixture was diluted with Et_2O (50 mL) and the precipitates were removed via filtration on a buchner funnel. The filtrate were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by

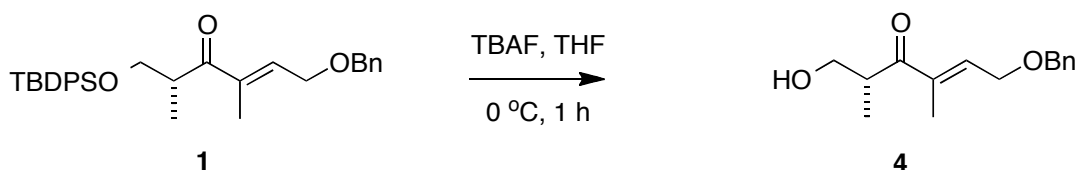
flash chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave enone **1** as a colorless oil (6.30 g, 12.9 mmol, 87%). $[\alpha]^{21}_{\text{D}} -19.1$ (c 0.83, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.64-7.60 (m, 4H), 7.41-7.26 (m, 11H), 6.72 (t, $J = 4.5$ Hz, 1H), 4.56 (s, 2H), 4.28-4.25 (m, 2H), 3.86-3.83 (m, 1H), 3.64-3.52 (m, 2H), 1.75 (s, 3H), 1.03 (d, $J = 6.0$ Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 204.6, 138.9, 137.9, 135.8, 135.8, 133.8, 133.6, 129.9, 128.8, 128.1, 128.1, 127.9, 73.3, 67.8, 67.2, 42.0, 27.0, 19.4, 14.7, 12.2. HRMS (ESI): Exact mass calcd for $\text{C}_{31}\text{H}_{39}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 487.2668. Found 487.2684.



To a solution of enone **1** (4.31 g, 8.86 mmol) in toluene (100 mL) cooled to -78 $^\circ\text{C}$ was added the neat DIBAL (3.16 mL, 17.7 mmol) in a period of 5 min. The reaction mixture was stirred for an additional 2 h before dropwise addition of anhydrous EtOAc (5 mL) at -78 $^\circ\text{C}$ and transferred quickly into a vigorously stirred mixture of EtOAc/saturated potassium sodium tartrate aqueous solution (300 mL/100 mL). Stirring was continued for 1 h and the layers were separated. The aqueous layer was extracted with EtOAc (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. ^1H NMR of the crude product suggested the *syn:anti* diastereoisomer ratio was 1.0:14. After purification by flash chromatography on silica gel, eluting with EtOAc/hexanes (10:90), the desired *anti*-allylic alcohol **2** can be obtained with 88% isolated yield and the *syn:anti* diastereoisomer ratio was further increased to $>99\%$ *de* (check by HPLC). $[\alpha]^{20.6}_{\text{D}} -14.0$ (c 0.71, CHCl_3); ^1H NMR (500 MHz, CDCl_3) δ 7.69-7.65 (m, 4H), 7.45-7.23 (m, 11H), 5.66 (t, $J = 7.5$ Hz, 1H), 4.51 (s, 2H), 4.11 (d, $J = 10.0$ Hz, 2H), 4.00 (d, $J = 10.0$ Hz, 1H), 3.90 (s, 1H), 3.80-3.78 (m, 1H), 3.67-3.63 (m, 1H), 1.96-1.89 (m, 1H), 1.64 (s, 3H), 1.06 (s, 9H), 0.73 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 140.0, 138.7, 135.8, 132.9, 128.1, 127.8, 124.8, 95.0, 83.2, 72.3, 69.2, 66.6, 37.5, 27.0, 19.3, 14.0, 11.8. HRMS (ESI): Exact mass calcd for $\text{C}_{31}\text{H}_{40}\text{NaO}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 511.2644. Found 511.2633.

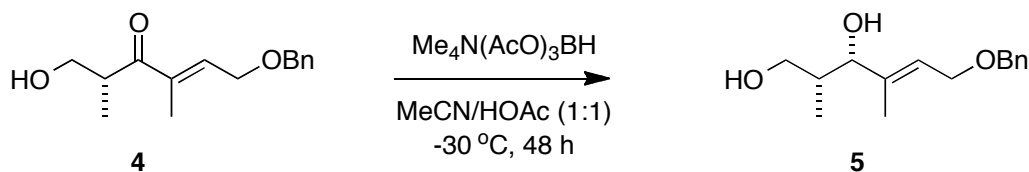


The allylic alcohol **2** (0.59 g, 1.2 mmol) was dissolved in THF (5 mL) followed by addition of TBAF (1M in THF, 1.4 mL, 1.4 mmol). The resulting solution was stirred at 25 °C for 1 h, then the reaction was quenched by addition of $\text{NH}_4\text{Cl(s)}$ (5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 5 mL). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (50:50) gave diol **3** (0.30 g, 1.2 mmol, 100%) as a colorless oil. $[\alpha]^{22.1}_{\text{D}} -11.0$ (c 1.09, CHCl_3); ^1H NMR (300 MHz, CDCl_3) 7.37-7.26 (m, 5H), 5.62 (t, $J = 6.0$ Hz, 1H), 4.52 (s, 2H), 4.08-4.02 (m, 2H), 3.92 (d, $J = 9.0$ Hz, 1H), 3.74-3.61 (m, 2H), 2.93 (br, 1H), 2.60 (br, 1H), 1.97-1.85 (m, 1H), 1.65 (s, 1H), 0.75 (d, $J = 9.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) 140.2, 138.4, 128.7, 128.1, 128.0, 125.1, 84.4, 72.7, 68.4, 66.5, 37.4, 14.0, 11.6. HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{22}\text{NaO}_3[\text{M}+\text{Na}]^+$ 273.1467. Found 273.1472.

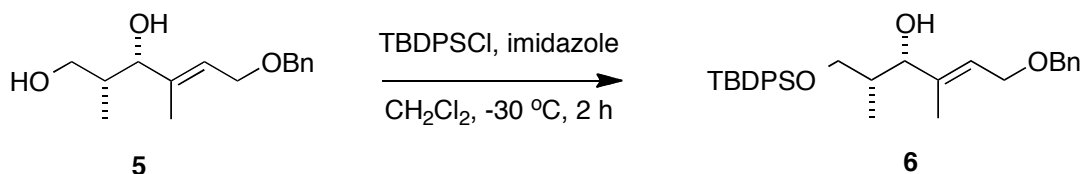


The enone **1** (4.78 g, 9.8 mmol) was dissolved in THF (100 mL) followed by addition of TBAF (1M in THF, 10.3 mL, 10.3 mmol). The resulting solution was stirred at 0 °C for 1 h, then the reaction was quenched by addition of $\text{NH}_4\text{Cl(s)}$ (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (30:70) gave enone **4** (1.60 g, 6.6 mmol, 67%) as a colorless oil. $[\alpha]^{22.2}_{\text{D}} -12.5$ (c 1.27, CHCl_3); ^1H NMR (300 MHz, CDCl_3) 7.41-7.26 (m, 5H), 6.78-6.72 (m, 1H), 4.58 (s, 2H), 4.30-4.22 (m, 2H), 3.92-3.64 (m, 2H), 3.47-3.35 (m, 1H), 2.21 (t, $J = 6.0$ Hz, 1H), 1.74 (s, 3H), 1.13 (d, $J = 9.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) 140.0, 137.8, 136.9, 128.8, 128.2, 128.1, 73.4, 67.7, 65.1, 41.5,

15.3, 12.1 (missing the peak for the carbonyl carbon). HRMS (ESI): Exact mass calcd for $C_{15}H_{21}O_3[M+H]^+$ 249.1491. Found 249.1488.

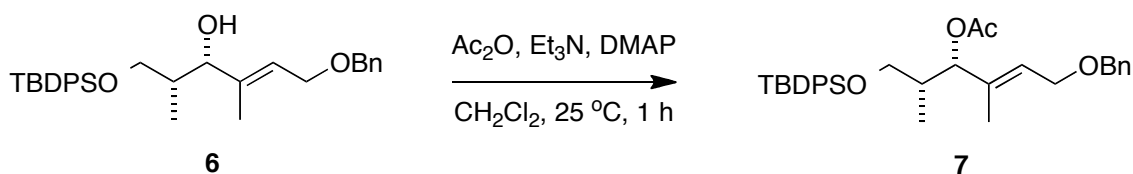


Tetramethylammonium triacetoxyborohydride (13.9 g, 52.8 mmol) was dissolved in $CH_3CN/AcOH$ (60 mL, 1:1) and the mixture was stirred for 30 min at 25 °C. The resulting clear solution was cooled to -30 °C and a solution of **4** in MeCN (6 mL, 2 x 2 mL for rinse) was added dropwise. The reaction mixture was stirred at -30 °C for an additional 48 h before dropwise addition of saturated potassium sodium tartrate aqueous solution (20 mL). Stirring was continued for 1 h and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were washed with $NaHCO_3(s)$ (30 mL), Brine (30 mL) and then dried with Na_2SO_4 . The solution was concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (50:50 to 80:20) gave diol **5** (1.40 g, 5.6 mmol, 81%) as a colorless oil. 1H NMR of the crude product indicated the *syn:anti* diastereoisomer ratio was >19:1.0. $[\alpha]^{21.9}_D$ -32.2 (*c* 0.62, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) 7.39-7.26 (m, 5H), 5.70 (t, *J* = 6.0 Hz, 1H), 4.53 (s, 2H), 4.18-4.08 (m, 3H), 3.72-3.64 (m, 2H), 2.07-1.83 (m, 3H), 1.63 (s, 3H), 0.91 (d, *J* = 9.0 Hz, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) 140.8, 138.6, 128.7, 128.1, 127.9, 78.4, 72.6, 67.1, 66.5, 37.7, 13.9, 10.6. HRMS (ESI): Exact mass calcd for $C_{15}H_{22}NaO_3[M+Na]^+$ 273.1467. Found 273.1463.

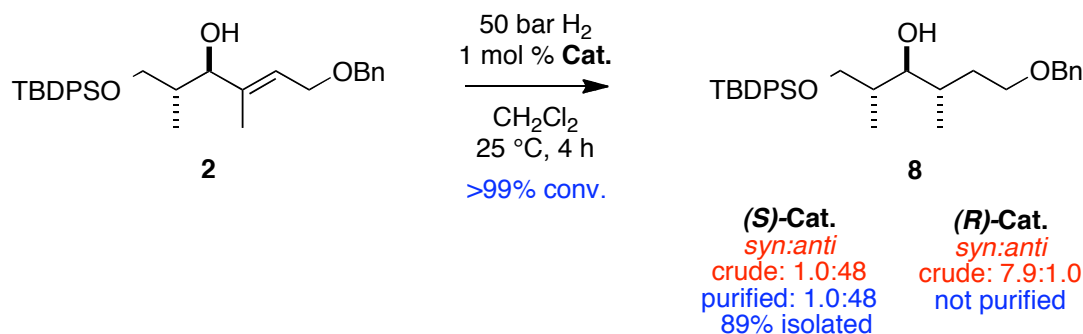


To a solution of compound **5** (0.88 g, 3.5 mmol) and imidazole (0.26 g, 3.85 mmol) in CH_2Cl_2 (10 mL) was added a solution of TBDPSCl (1.02 g, 3.7 mmol) in CH_2Cl_2 (5 mL, 2 x 1 mL for rinse) dropwise at -30 °C. The reaction was stirred for 2 h, then quenched with $NaHCO_3(s)$ (10 mL). The organic layer was separated and the aqueous layer was

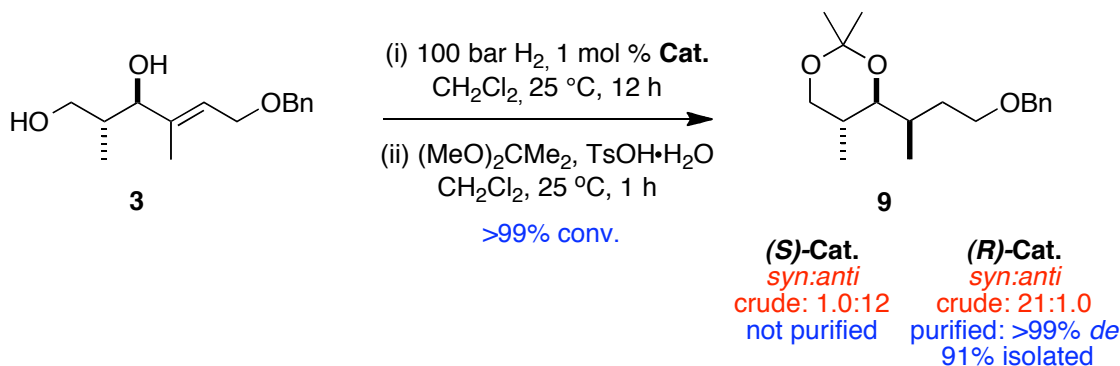
extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (20:80) gave alcohol **6** (1.30 g, 2.7 mmol, 76%) as a colorless oil. $[\alpha]^{22.2}_{\text{D}} -15.0$ (c 0.80, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.70-7.65 (m, 4H), 7.47-7.26 (m, 11H), 5.74 (t, $J = 6.0$ Hz, 1H), 4.51 (s, 2H), 4.28 (m, 1H), 4.11 (d, $J = 6.0$ Hz, 2H), 3.72-3.64 (m, 2H), 2.42 (d, $J = 3.0$ Hz, 1H), 1.91-1.82 (m, 1H), 1.58 (s, 3H), 1.08 (s, 9H), 0.90 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) 140.2, 138.7, 135.8, 133.4, 130.0, 128.0, 127.8, 121.9, 77.4, 72.3, 67.9, 66.5, 37.9, 27.1, 19.5, 13.8, 10.5. HRMS (ESI): Exact mass calcd for $\text{C}_{31}\text{H}_{41}\text{O}_3\text{Si}[\text{M}+\text{H}]^+$ 489.2825. Found 489.2848.



To a solution of compound **6** (0.86 g, 1.75 mmol) and DMAP (22 mg, 0.18 mmol) in CH_2Cl_2 (10 mL) was added Ac_2O (0.33 mL, 3.5 mmol) and Et_3N (0.49 mL, 3.5 mmol) dropwise at 25°C . The reaction was stirred for 1 h, and then quenched with NaHCO_3 (s) (5 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with EtOAc/hexanes (5:95) gave acetate **7** (0.85 g, 1.6 mmol, 92%) as a colorless oil. $[\alpha]^{20.8}_{\text{D}} -20.6$ (c 0.87, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.67-7.60 (m, 4H), 7.43-7.26 (m, 11H), 5.53 (t, $J = 6.0$ Hz, 1H), 4.44 (s, 2H), 4.11-3.97 (m, 2H), 3.49 (d, $J = 9.0$ Hz, 2H), 2.05 (s, 3H), 2.04-1.96 (m, 1H), 1.56 (s, 3H), 1.05 (s, 9H), 0.89 (d, $J = 9.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) 170.3, 138.5, 136.4, 135.9, 135.8, 133.9, 133.8, 127.8, 123.6, 77.8, 77.5, 72.1, 66.3, 65.6, 37.7, 27.1, 21.3, 19.5, 13.8, 11.7. HRMS (ESI): Exact mass calcd for $\text{C}_{33}\text{H}_{42}\text{NaO}_4\text{Si}[\text{M}+\text{Na}]^+$ 553.2750. Found 553.2765.

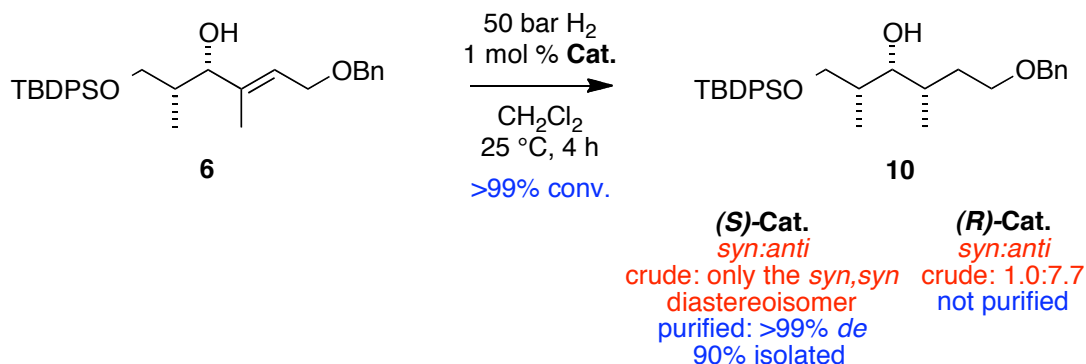


Hydrogenation of **2** (175 mg, 0.36 mmol) was carried out according to the general procedure using **(S)-Cat.** (1 mol%, 6 mg) in CH_2Cl_2 (0.72 mL). NMR of the crude product showed 100% reduction. HPLC analysis of the crude material showed *syn:anti* ratio to be 1.0:48. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (5:95) give *anti,anti* triad **8** (*syn:anti* = 1.0:48 from HPLC analysis) as a colorless oil (155 mg, 0.32 mmol, 89%). $[\alpha]^{20.8}_D$ -21.7 (*c* 0.92, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.72-7.66 (m, 4H), 7.49-7.27 (m, 11H), 4.57 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.0 Hz, 1H), 3.80-3.36 (m, 6H), 1.99-1.79 (m, 3H), 1.61-1.53 (m, 1H), 1.07 (s, 9H), 0.99 (d, *J* = 6.0 Hz, 3H), 0.87 (d, *J* = 9.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 138.9, 135.8, 133.1, 130.1, 128.6, 128.0, 128.0, 127.8, 127.7, 81.1, 73.1, 69.2, 69.0, 37.5, 33.2, 30.3, 27.1, 19.4, 17.3, 14.2. HRMS (ESI): Exact mass calcd for $C_{31}H_{43}O_3Si[M+H]^+$ 491.2981. Found 491.3002.



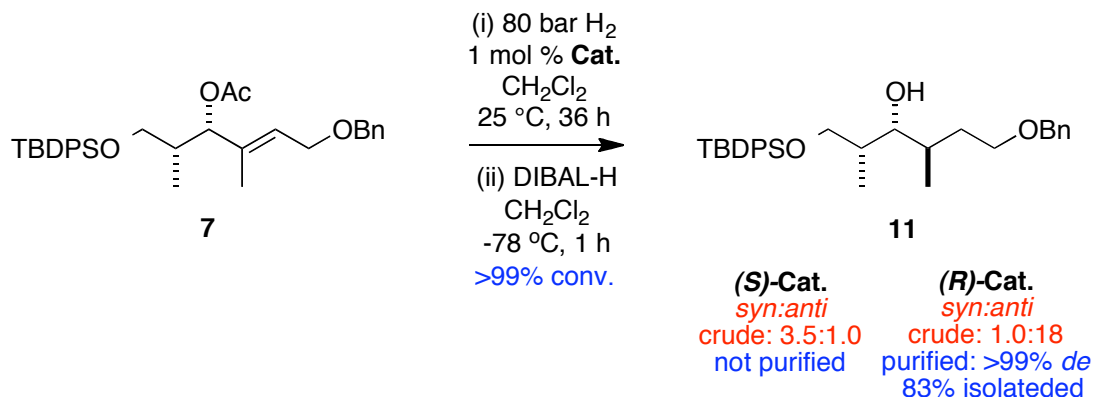
Hydrogenation of **3** (310 mg, 1.2 mmol) was carried out according to the general procedure using **(R)-Cat** (1 mol%, 19 mg) in CH_2Cl_2 (1 mL). NMR of the crude product showed 100% conversion. Thus without purification, the crude diol was dissolved in CH_2Cl_2 (10 mL). $TsOH$ (22.8 mg, 0.12 mmol) and 2,2-Dimethoxypropane (0.74 mL, 6.0

mmol) were then added to the solution of diol and the resulting mixture was stirred for 1 h at 25 °C. The reaction was quenched by adding NaHCO₃(s) (5 mL). The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. HPLC analysis of the crude material showed *syn:anti* ratio to be 21:1.0. Purification by column chromatography EtOAc/hexanes (5:95) gave the *anti,syn* triad **9**² as a colorless oil (319 mg, 91% from **3**, HPLC analysis showed *syn:anti* >99% *de*). [α]^{21.1}_D -34.7 (*c* 0.92, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.28 (m, 5H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.70-3.65 (m, 1H), 3.56-3.36 (m, 4H), 1.97-1.60 (m, 4H), 1.34 (s, 3H), 1.33 (s, 3H), 0.88 (d, *J* = 6.0 Hz, 3H), 0.72 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 138.9, 128.6, 128.0, 127.8, 98.3, 76.7, 73.2, 68.4, 66.7, 33.8, 31.1, 30.1, 29.9, 19.2, 12.7, 12.5.

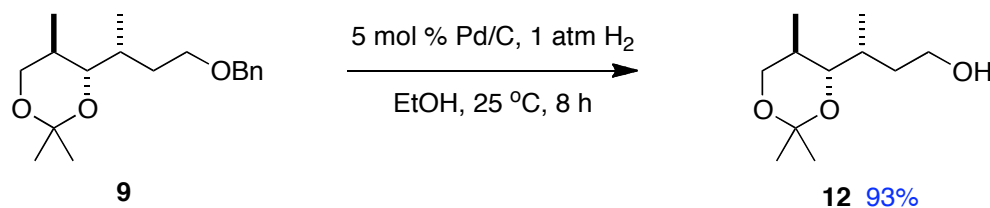


Hydrogenation of **6** (250 mg, 0.50 mmol) was carried out according to the general procedure using **(S)-Cat.** (1 mol%, 8 mg) in CH₂Cl₂ (1.0 mL). NMR of the crude product showed 100% reduction to **10**. HPLC analysis of the crude material can only detect the *syn,syn* triad. One simple column chromatography on silica gel, eluting with EtOAc/hexanes (5:95) give *syn,syn* triad **10** as a colorless oil (230 mg, 0.45 mmol, 90%). [α]^{21.1}_D -8.9 (*c* 0.89, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 7.71-7.65 (m, 4H), 7.48-7.29 (m, 11H), 4.53 (d, *J* = 12.0 Hz, 1H), 4.49 (d, *J* = 12.0 Hz, 1H), 3.73-3.47 (m, 5H), 2.72 (d, *J* = 3.0 Hz, 1H), 1.91-1.69 (m, 3H), 1.46-1.37 (m, 1H), 1.08 (s, 9H), 1.01 (d, *J* = 6.0 Hz, 3H), 0.96 (d, *J* = 6.0 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 138.6, 135.8, 133.4, 130.0, 130.0, 128.6, 128.0, 127.9, 127.8, 77.5, 73.3, 68.8, 68.6, 37.2, 33.6, 33.5, 27.1,

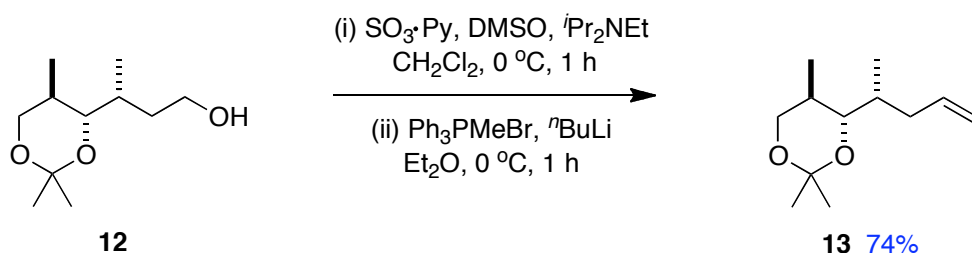
19.5, 15.1, 11.3. HRMS (ESI): Exact mass calcd for $C_{31}H_{43}O_3Si[M+H]^+$ 491.2981. Found 491.2995.



Hydrogenation of **7** (440 mg, 0.83 mmol) was carried out according to the general procedure using **(R)-Cat** (1 mol%, 15 mg) in CH_2Cl_2 (1.5 mL). NMR of the crude product showed 100% conversion. Thus without purification, the crude acetate was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. DIBAL-H (1.0 M in Hexanes, 2.0 mL, 2.0 mmol) was added dropwise and the solution was stirred at -78 °C for 1 h. EtOAc (2 mL) was added to the mixture followed by addition of saturated potassium sodium tartrate aqueous solution (5 mL). Stirring was continued for 1h and the layers were separated. The aqueous layer was extracted with EtOAc (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. HPLC analysis of the crude material showed *syn:anti* ratio to be 1.0:18. Purification by column chromatography EtOAc/hexanes (5:95) gave the *syn,anti* triad **11** as a colorless oil (340 mg, 0.69 mmol, 83% from **7**, HPLC analysis showed *syn:anti* >99% *de*). $[\alpha]^{21.4}_D -5.5$ (*c* 1.08, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.65 (m, 4H), 7.45-7.28 (m, 11H), 4.55 (d, $J = 12.0$ Hz, 1H), 4.51 (d, $J = 12.0$ Hz, 1H), 3.73-3.51 (m, 5H), 3.00 (d, $J = 3.0$ Hz, 1H), 1.99-1.51 (m, 4H), 1.08 (s, 9H), 0.93 (d, $J = 6.0$ Hz, 3H), 0.85 (d, $J = 6.0$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 138.7, 135.9, 133.6, 130.0, 129.9, 128.6, 127.9, 127.9, 127.8, 77.5, 73.2, 68.9, 68.9, 37.0, 34.3, 33.4, 27.2, 19.5, 16.7, 9.6. HRMS (ESI): Exact mass calcd for $C_{31}H_{43}O_3Si[M+H]^+$ 491.2981. Found 491.2969.

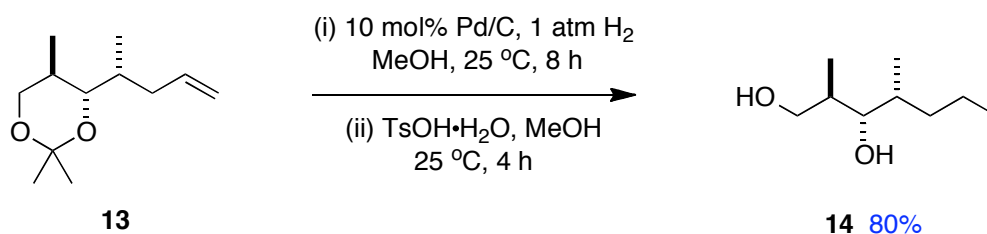


To a solution of **9** (1.06 g, 3.64 mmol) in MeOH (20 mL) was added Pd/C (10% on carbon, 194 mg, 0.18 mmol) in one portion. The air inside the reaction flask was vacuumed out and then hydrogen gas was purged into the flask. The mixture was stirred under 1 atm H₂ pressure at rt for 8 h. The mixture was filtered on a plug of silica gel (5 cm), washed with MeOH, and concentrated to give 0.68 g (93%) of free saturated alcohol **12** as a colorless oil. $[\alpha]^{22.0}_{\text{D}} -42.8$ (*c* 0.70, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 3.78-3.65 (m, 3H), 3.61-3.46 (m, 2H), 2.14-2.10 (m, 1H), 2.01-1.89 (m, 2H), 1.85-1.59 (m, 2H), 1.43 (s, 3H), 1.38 (s, 3H), 0.93 (d, *J* = 6.0 Hz, 3H), 0.75 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 98.5, 77.9, 66.5, 60.4, 37.3, 31.1, 30.8, 29.9, 19.3, 12.7, 12.4. HRMS (ESI): Exact mass calcd for C₁₁H₂₃O₃[M+H]⁺ 203.1647. Found 203.1654.



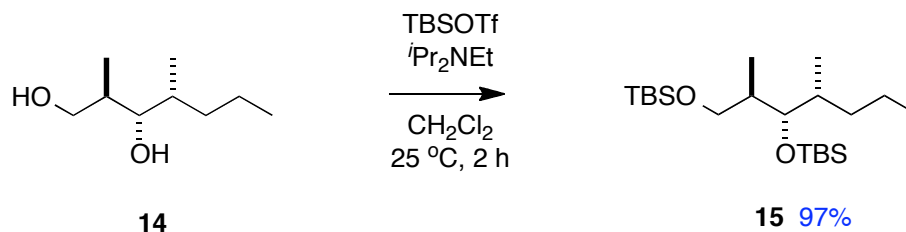
The alcohol **12** (0.68 g, 2.0 mmol) was dissolved in CH₂Cl₂ (60 mL) at 0 °C. DMSO (6.0 mL, 84.5 mmol) and DIPEA (5.9 mL, 33.8 mmol) were added. To this solution at 0 °C, SO₃·Py complex (2.69 g, 16.9 mmol) was added and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched with NH₄Cl (20 mL). The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL). The combined organic solution was dried (Na₂SO₄) and concentrated *in vacuo*. The resulting residue was carried out to the next step without any further purification. In a separate round bottom flask, methyltriphenylphosphonium bromide (2.41 g, 6.76 mmol) suspension in THF (20 mL) was cooled to 0 °C and ⁿBuLi (2.0 M in Pentane, 3.4 mL, 6.8 mmol) was added dropwise. The reaction was stirred for 0.5 h before the crude aldehyde in THF solution (8 mL, 2 x 1 mL for rinsing) was cannulated. After 1 h, saturated NH₄Cl

aqueous solution (10 mL) was added and the mixture was stirred and allowed to warm to 25 °C. The layers were then separated and the aqueous layer was extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* at 10 °C. Purification by flash column chromatography, eluting with Et₂O/pentane (5:95) gave alkene **13** (0.49 g, 74% over two steps) as a colorless oil. $[\alpha]^{19.6}_D$ -27.1 (*c* 0.81, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 5.86-5.72 (m, 1H), 5.06-4.96 (m, 2H), 3.71 (dd, *J* = 3.0, 12.0 Hz, 1H), 3.54-3.45 (m, 2H), 2.22-1.70 (m, 1H), 1.71-1.31 (m, 12H), 1.13 (d, *J* = 10.0 Hz, 3H), 1.10-1.01 (m, 2H), 0.91-0.86 (m, 6H), 0.78-0.76 (m, 4H), 1.40 (s, 3H), 1.38 (s, 3H), 0.90 (d, *J* = 9.0 Hz, 3H), 0.71 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.2, 116.0, 98.3, 76.2, 66.7, 38.5, 33.6, 31.1, 30.0, 19.3, 12.8, 12.5. HRMS (ESI): Exact mass calcd for C₁₂H₂₃O₂[M+H]⁺ 199.1698. Found 199.1670.

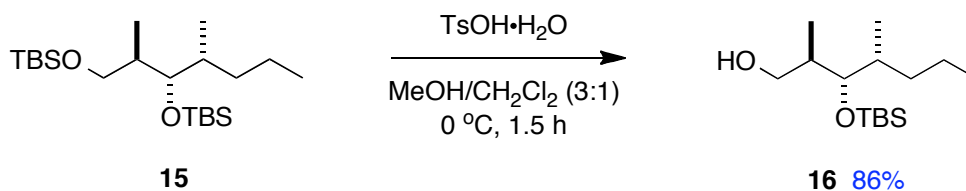


To a solution of **13** (0.49 g, 2.5 mmol) in MeOH (10 mL) was added Pd/C (10% on carbon, 266 mg, 0.25 mmol) in one portion. The air inside the reaction flask was vacuumed out and then hydrogen gas was purged into the flask. The mixture was stirred under 1 atm H₂ pressure at rt for 8 h. The mixture was filtered on a plug of silica gel (5 cm) and washed with MeOH (5 mL). To the filtrate the TsOH (48 mg, 0.25 mmol) was added in one portion and the solution was stirred for 4 h at 25 °C. The reaction mixture was quenched with saturated aqueous NaHCO₃ (5 mL), extracted with ether (3 × 10 mL), dried over MgSO₄, and concentrated. Purification by column chromatography (silica gel, EtOAc/hexanes, 50:50) gave 0.32 g (80%, 2 steps) of diol **14** as a colorless liquid; $[\alpha]^{21.7}_D$ -21.9 (*c* 0.73, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 3.79-3.63 (m, 2H), 3.53-3.47 (m, 1H), 2.94-2.91 (m, 1H), 2.34 (d, *J* = 6.0 Hz, 1H), 1.96-1.82 (m, 1H), 1.67-1.60 (m, 1H), 1.41-1.24 (m, 4H), 0.94 (t, *J* = 6.0 Hz, 3H), 1.72-1.41 (m, 9H), 1.08 (d, *J* = 7 Hz, 3H), 1.07 (m, 1H), 1.06 (m, 1H), 0.93 (d, *J* = 7 Hz, 3H), 0.90 (d, *J* = 9.0 Hz, 3H), 0.84 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 80.7, 69.1, 37.7, 36.5, 35.1, 20.7, 14.5,

13.8, 12.5; HRMS (ESI): Exact mass calcd for $C_9H_{21}O_2$ $[M+H]^+$: 161.1542, found: 161.1535.

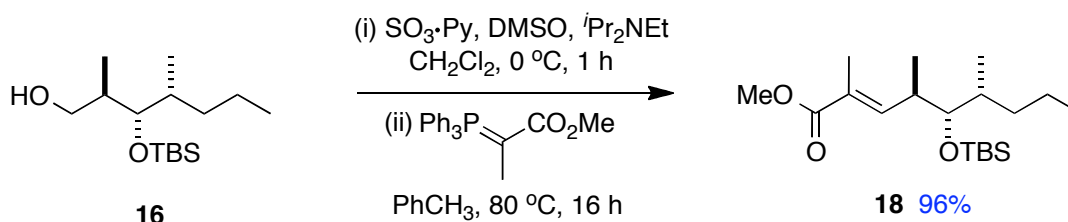


The diol **14** (0.32 g, 2.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and TBSOTf (1.15 mL, 5.0 mmol) and iPr_2NEt (1.05 mL, 6.0 mmol) were added sequentially. The solution was stirred at 25 °C for 2 h, then the reaction was quenched by adding $NH_4Cl(s)$ (10 mL). The mixture was diluted with CH_2Cl_2 (10 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, hexanes) gave **15** (0.75 g, 1.94 mmol, 97%) as a colorless liquid. $[\alpha]^{20.9}_D +12.3$ (c 0.65, $CHCl_3$); 1H NMR (500 MHz, $CDCl_3$) δ 3.70 (dd, $J = 5.0, 10.0$ Hz, 1H), 3.51-3.50 (m, 1H), 3.42 (dd, $J = 5.0, 10.0$ Hz, 1H), 1.83-1.78 (m, 1H), 1.63-1.53 (m, 1H), 1.34-1.13 (m, 4H), 0.91-0.89 (m, 36H), 0.86 (d, $J = 5.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 77.2, 65.9, 40.6, 37.4, 36.0, 26.4, 26.2, 26.0, 21.0, 18.6, 14.8, 14.6, 14.5, -2.7, -3.6, -3.7, -5.0, -5.1. HRMS (ESI): Exact mass calcd for $C_{21}H_{49}O_2Si[M+H]^+$ 389.3271. Found 389.3257.

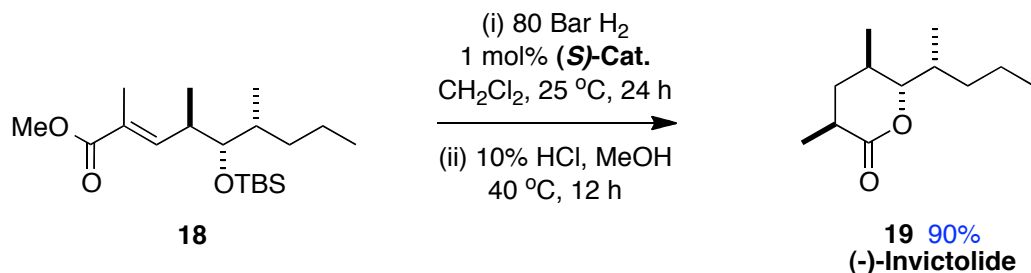


The silyl ether **15** (0.70 g, 1.8 mmol) was dissolved in $CH_2Cl_2/MeOH$ (20 mL, 1/3) at 0 °C. TsOH (34 mg, 0.18 mmol) was added in one portion. The resulting solution was stirred at that temperature for 1 h. Et_3N (5 mL) was then added to the reaction and all the solvents were evaporated under vacuum. The residue was purified through column chromatography, eluting with $EtOAc$ /hexanes (10:90) to give desired primary alcohol **16** (0.42 g, 1.55 mmol, 86%) as a colorless liquid. $[\alpha]^{21.5}_D 13.9$ (c 1.15, $CHCl_3$); 1H NMR

(500 MHz, CDCl_3) δ 3.68-3.58 (m, 2H), 3.52 (dd, $J = 5.0, 10.0$ Hz, 1H), 2.63 (t, $J = 7.5$ Hz, 1H), 1.91-1.84 (m, 1H), 1.66-1.61 (m, 1H), 1.47-1.37 (m, 2H), 1.24-1.13 (m, 2H), 0.98 (d, $J = 5.0$ Hz, 3H), 0.94-0.90 (m, 15H), 0.13 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 81.5, 66.5, 38.4, 37.8, 35.6, 26.3, 21.1, 18.5, 16.6, 15.4, 14.6, -3.7, -3.9; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{35}\text{O}_2\text{Si}$ $[\text{M}+\text{H}]^+$: 275.2406, found: 275.2419.



The alcohol **16** (275 mg, 1.0 mmol) was dissolved in CH_2Cl_2 (30 mL) at 0 °C. DMSO (0.11 mL, 1.5 mmol) and DIPEA (0.87 mL, 5.0 mmol) were added. To this solution at 0 °C, $\text{SO}_3\cdot\text{Py}$ complex (478 mg, 3.0 mmol) was added and the resulting solution was stirred at that temperature for 1 h. The reaction was quenched with NH_4Cl (10 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. Without any further purification, the resulting crude aldehyde was immediately dissolved in toluene (10 mL) and the Wittig reagent (1.74 g, 5.0 mmol) was added in one portion at 25 °C. The reaction mixture was then put on an oil bath (preheated to 80 °C) and stirred for 16 h. After being cooled to 25 °C, the reaction mixture was diluted with hexanes (80 mL) and filtrated through Celite. The filtrate was concentrated and purification of the residue by flash chromatography on silica gel, eluting with EtOAc/hexanes (5:95) gave alkene **18** as a colorless oil (300 mg, 0.88 mmol, 88%). $[\alpha]_D^{21}$ 20.9 (c 0.86, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 6.85 (d, $J = 9.0$ Hz, 5H), 3.76 (s, 3H), 3.50-3.46 (m, 1H), 2.77-2.65 (m, 1H), 1.86 (s, 3H), 1.39-1.00 (m, 4H), 0.93 (d, $J = 6.0$ Hz, 3H), 0.90 (s, 9H), 0.91-0.88 (m, 3H), 0.87 (t, $J = 9.0$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.1, 146.6, 126.3, 79.7, 51.9, 37.5, 37.5, 36.2, 26.3, 21.0, 18.1, 15.0, 14.5, 12.8, -3.5, -3.7. HRMS (ESI): Exact mass calcd for $\text{C}_{19}\text{H}_{39}\text{O}_3\text{Si}$ $[\text{M}+\text{H}]^+$ 343.2668. Found 343.2679.



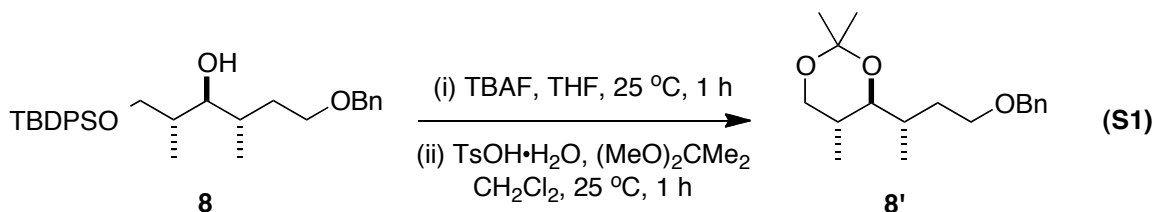
Hydrogenation of **18** (200 mg, 0.58 mmol) was carried out according to the general procedure using **(S)-Cat.** (1 mol%, 10 mg) in CH_2Cl_2 (1.0 mL). NMR of the crude product showed 100% reduction. ^1H NMR analysis of the crude material showed >19:1.0 diastereoselectivity for the hydrogenation. After hydrogenation the solvent was evaporated. Then the crude oil was dissolved in MeOH (4 mL) followed by addition of 10% HCl(aq) (0.2 mL). The resulting solution was stirred at 40 $^\circ\text{C}$ for 12 h, and then the reaction was cooled to 25 $^\circ\text{C}$ and quenched by addition of $\text{NaHCO}_3(\text{s})$ (5 mL). The solution was diluted by addition of Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (3 x 10 mL). The organic extract was dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash column chromatography, eluting with Et_2O /pentane (10:90) gave (-)-invictolide **19**³ (104 mg, 0.52 mmol, 90%) as a colorless oil. $[\alpha]_D^{21} -99.7$ (*c* 0.77, CHCl_3) {lit⁴ $[\alpha]_D -99.2$ (*c* 0.7, CHCl_3)}; ^1H NMR (500 MHz, CDCl_3) δ 3.92 (d, *J* = 10.0 Hz, 1H), 2.69-2.62 (m, 1H), 2.05-1.95 (m, 1H), 1.69 (t, *J* = 10.0 Hz, 2H), 1.38-1.27 (m, 5H), 1.23 (d, *J* = 10.0 Hz, 3H), 0.99 (d, *J* = 5.0 Hz, 3H), 0.92 (t, *J* = 5.0 Hz, 3H), 0.88 (d, *J* = 12.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.7, 85.7, 36.1, 35.4, 33.6, 32.5, 28.4, 20.4, 16.6, 14.1, 12.3. HRMS (ESI): Exact mass calcd for $\text{C}_{12}\text{H}_{23}\text{O}_2[\text{M}+\text{H}]^+$ 199.1698. Found 199.1691.

Table S-1. Comparison of ^{13}C NMR of **(-)-invictolide**

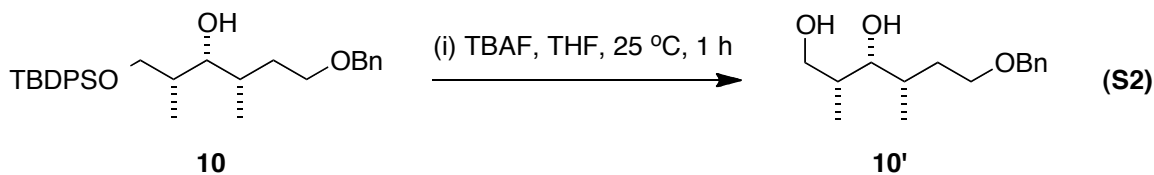
atom number	previous synthesis ³ of (-)-invictolide ($\delta\text{c ppm}$)	this work: (-)-invictolide ($\delta\text{c ppm}$)
C1	12.2	12.3
C2	14.1	14.1
C3	16.5	16.5
C4	17.6	17.6
C5	20.4	20.4
C6	28.3	28.4
C7	32.5	32.5
C8	33.5	33.6
C9	35.3	35.4
C10	36.0	36.1
C11	85.6	85.7
C12	176.8	176.7

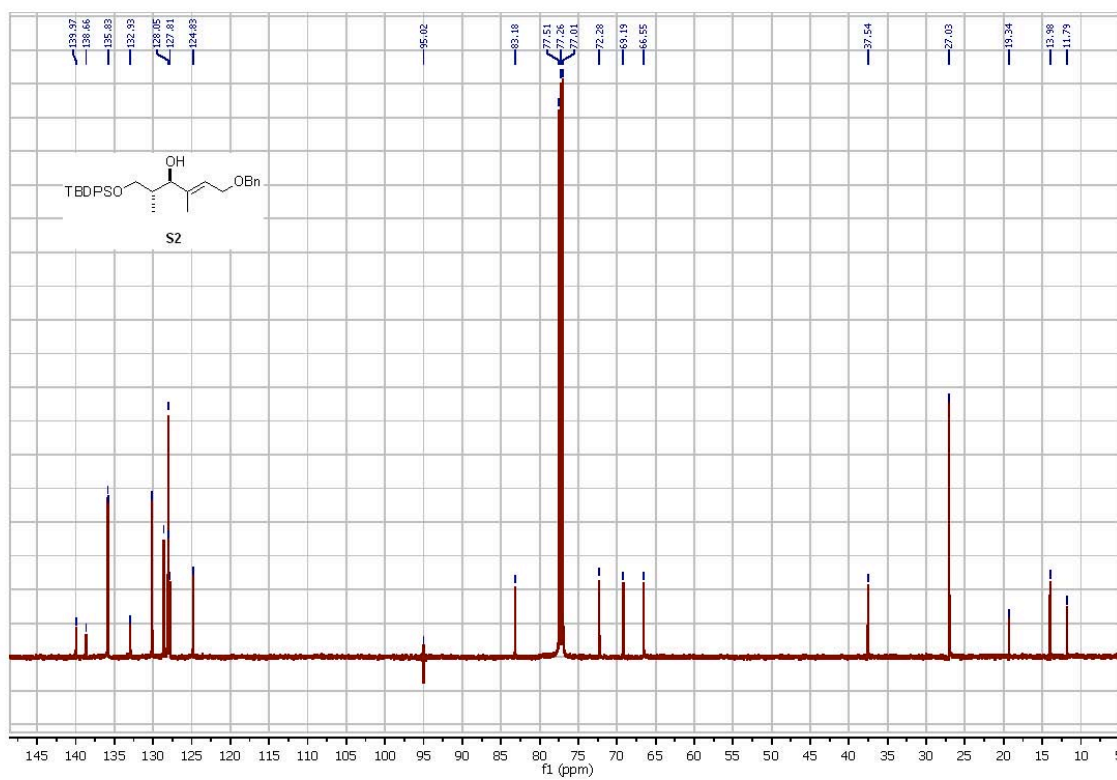
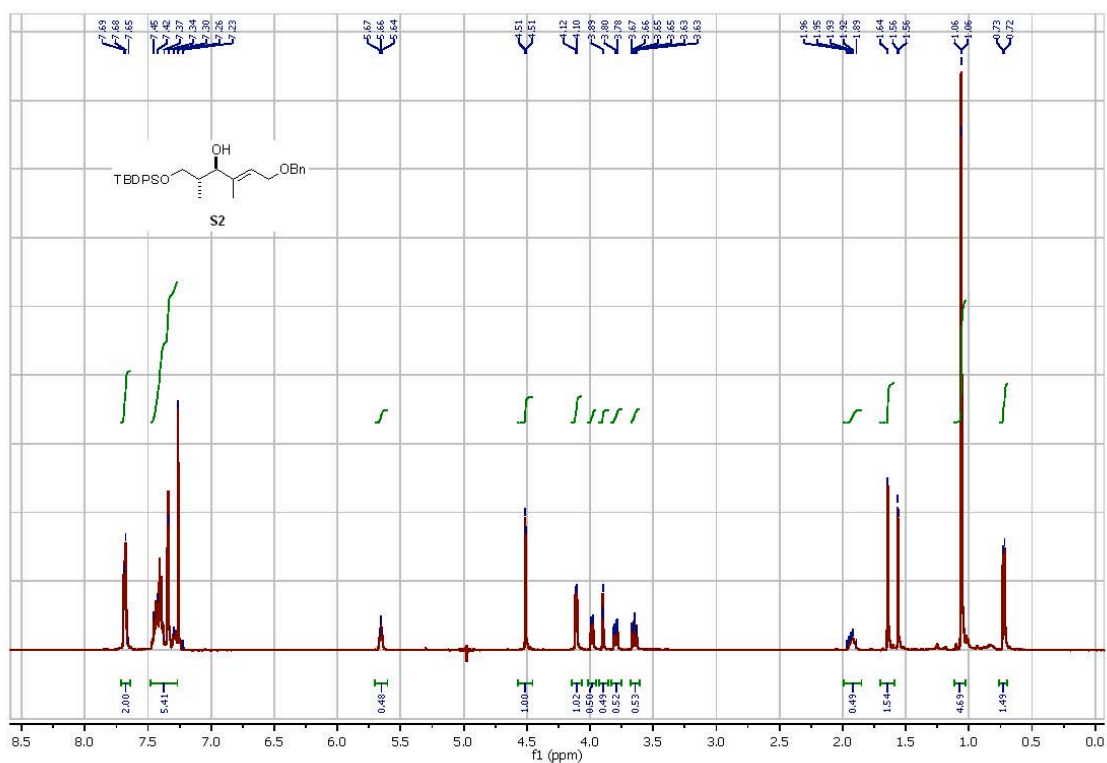
Relative and absolute configuration determination

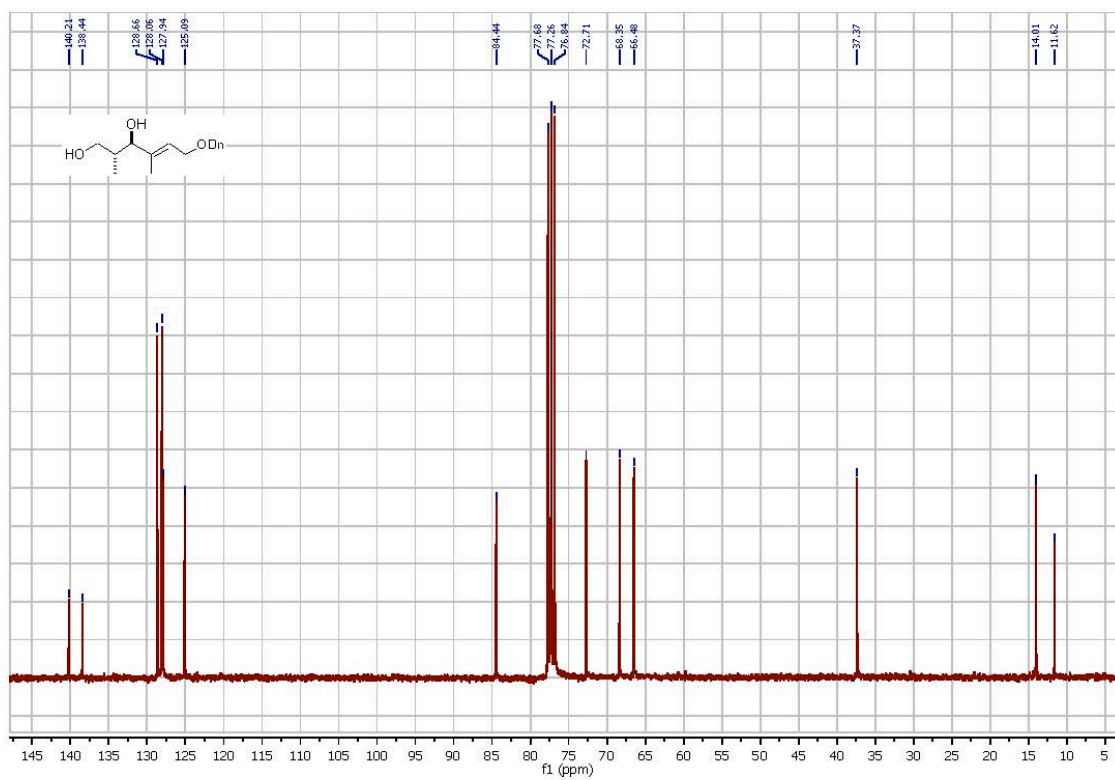
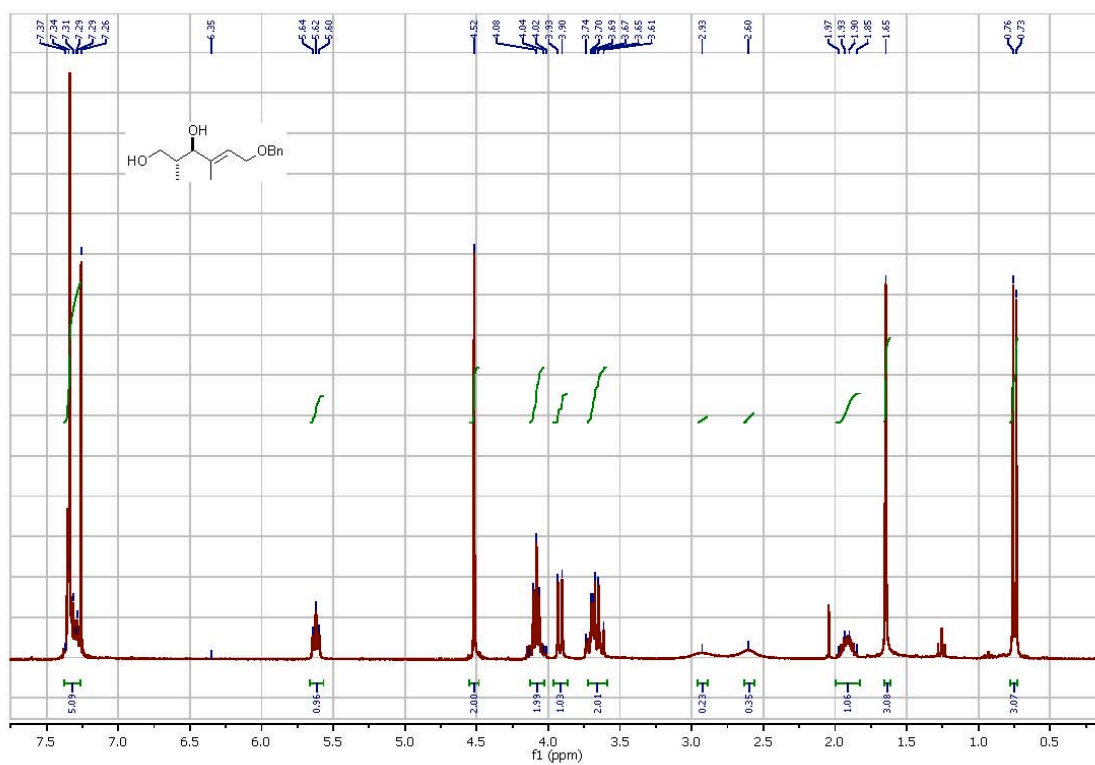
All the alkene substrates were made from enantiomer enriched (*R*)-*Roche ester* (98% *ee*). So the absolute stereochemistry was determined by the chirality from the starting material. Hydrogenation of **2** with (*S*)-Cat provided the triad **8** with high diastereoselectivity (*syn:anti*, *dr* 1.0:48). Starting from **8**, an acetonide derivative **8'** can be synthesized in two steps (Reaction S1). **8'** was a known compound with reported ¹H NMR and ¹³C NMR.² Thus **8**, the hydrogenation product of **2**, was determined to be an *anti,anti* stereotriad. Hydrogenation of **3** with (*R*)-Cat provided the triad **9** with high diastereoselectivity (*syn:anti*, *dr* 21:1.0). The isolated product **9** was also a known compound with reported ¹H NMR and ¹³C NMR data.² Hence **9** was determined to be the *anti,syn* stereotriad undoubtedly.

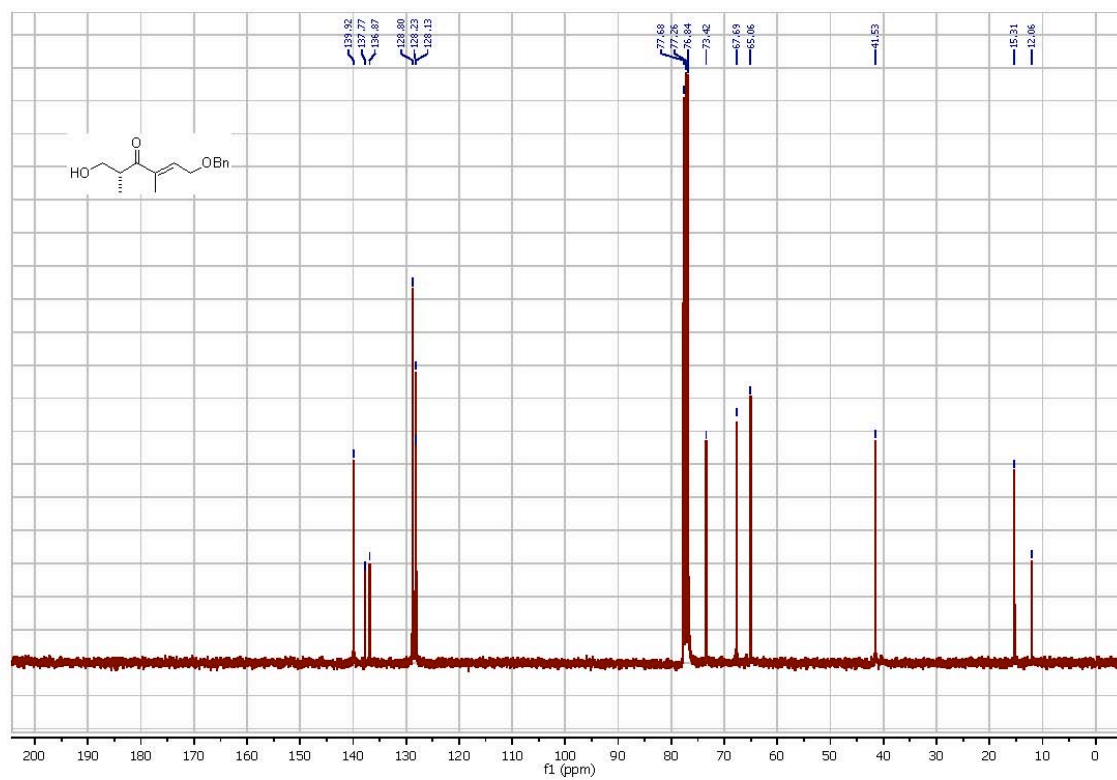
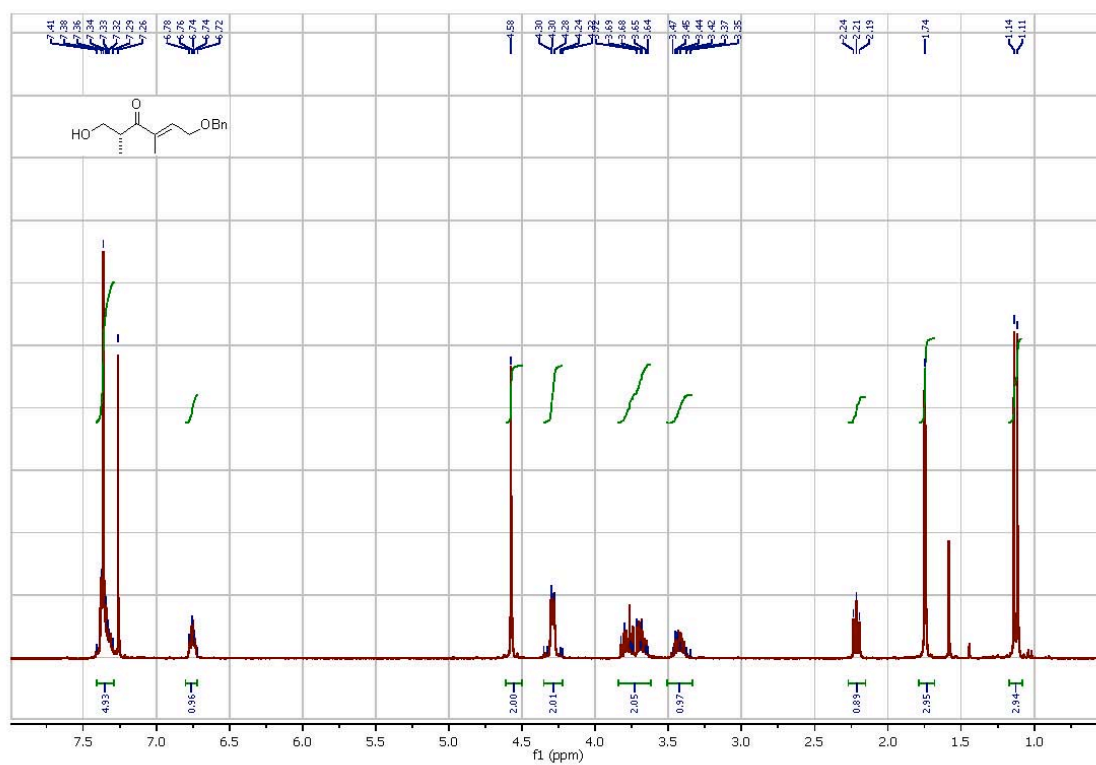


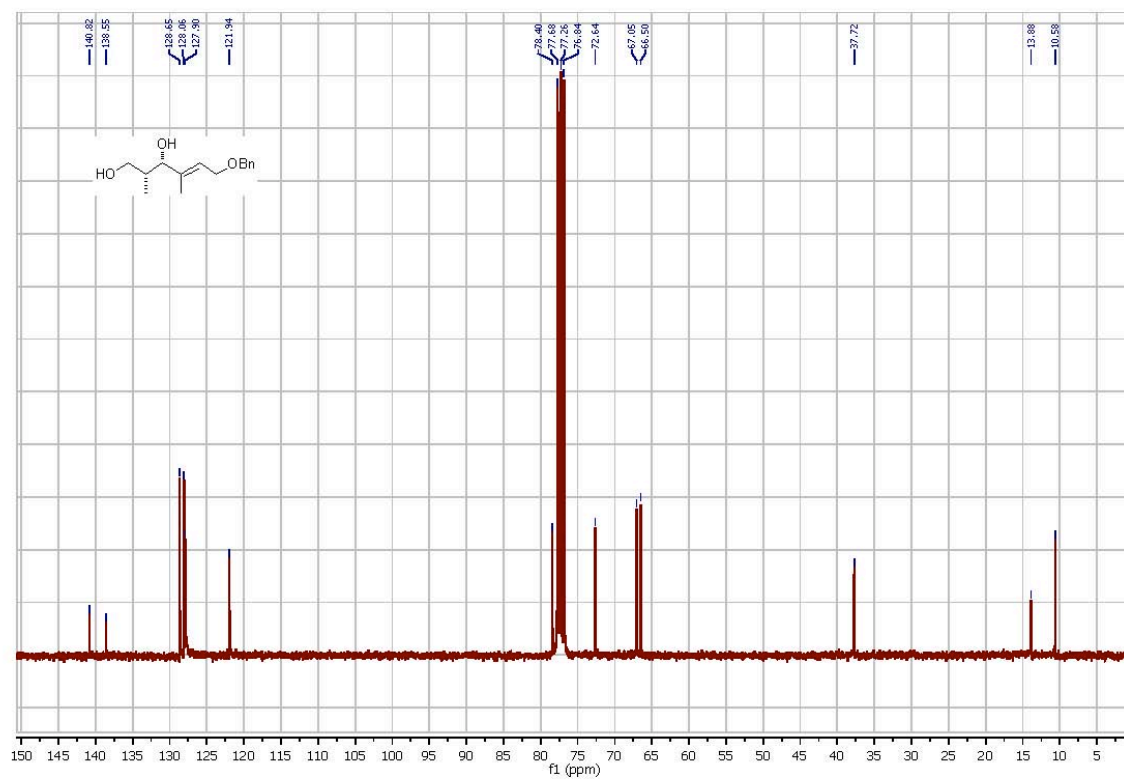
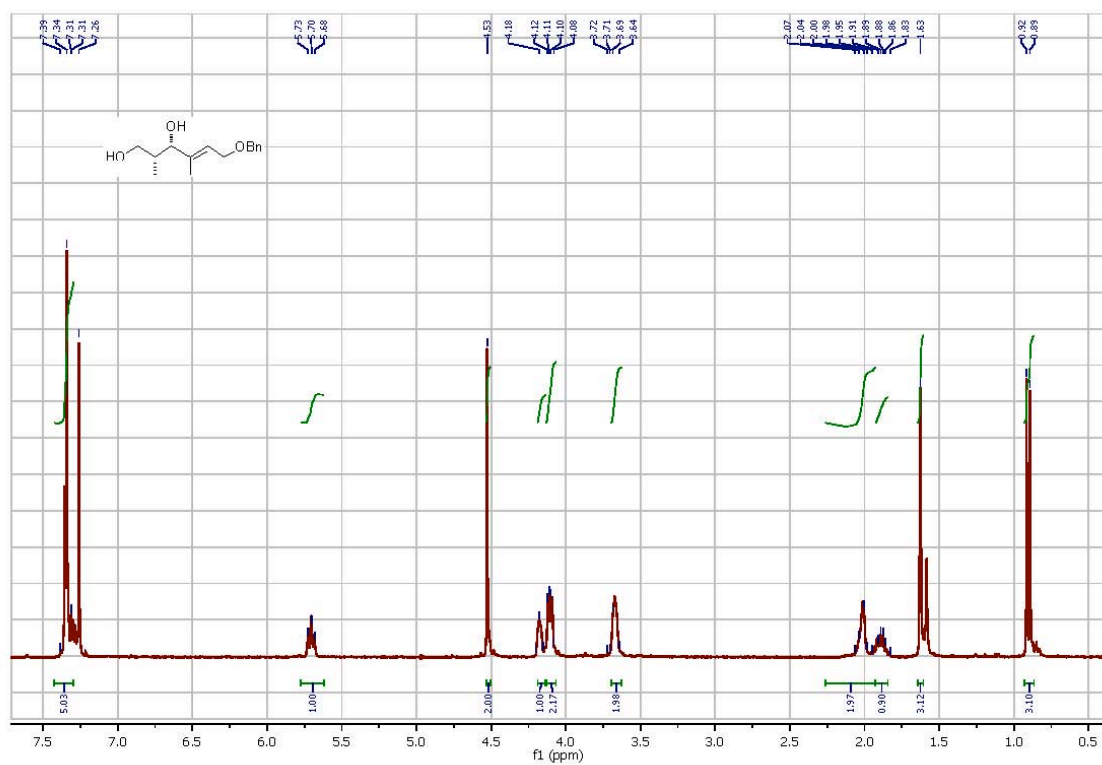
Hydrogenation of **6** with (*S*)-Cat provided the triad **10** with high diastereoselectivity (*syn:anti*, *dr* >99:1.0). Starting from **10**, the diol **10'** can be synthesized in one step (Reaction S2). **10'** was a known compound with reported ¹H NMR and ¹³C NMR data.⁵ Thus **10**, the hydrogenation product of **6**, was determined to be an *syn,syn* stereotriad. Hydrogenation of **7** with (*R*)-Cat provided the triad **11** with high diastereoselectivity (*syn:anti*, *dr* 1.0:18). The ¹H NMR and ¹³C NMR of the isolated product **11** was compared carefully with those of **8** and **10**.² Hence **11** was determined to be the *syn,anti* stereotriad certainly.

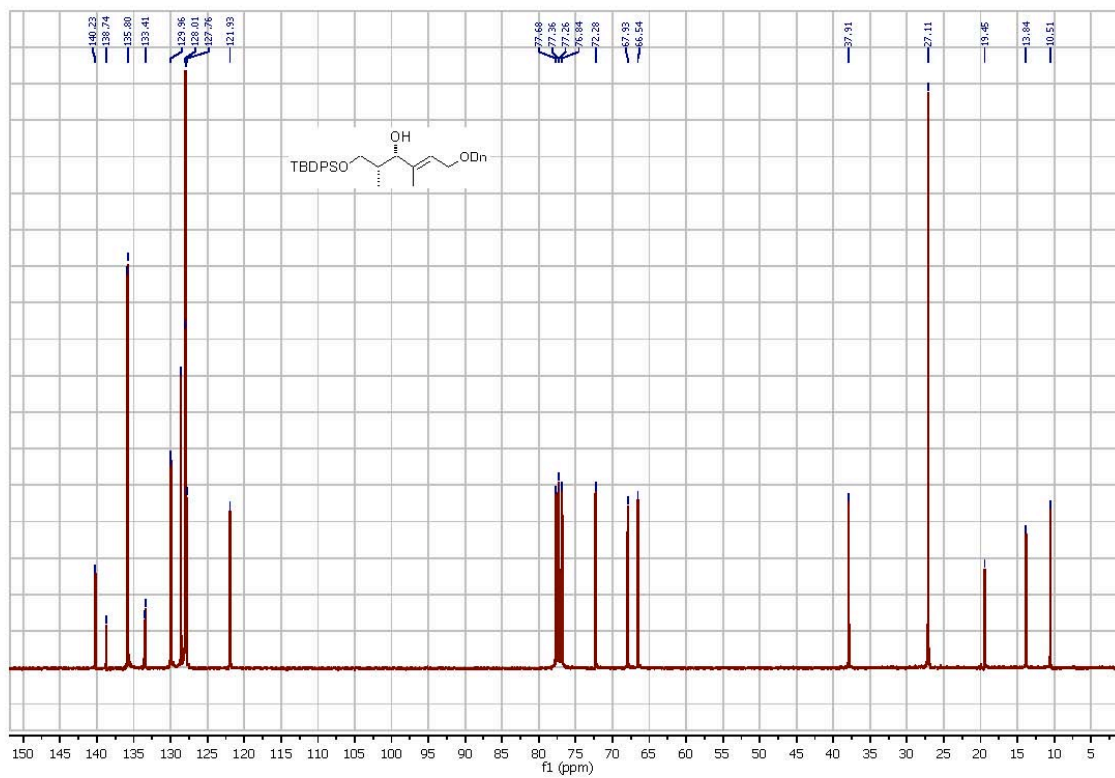
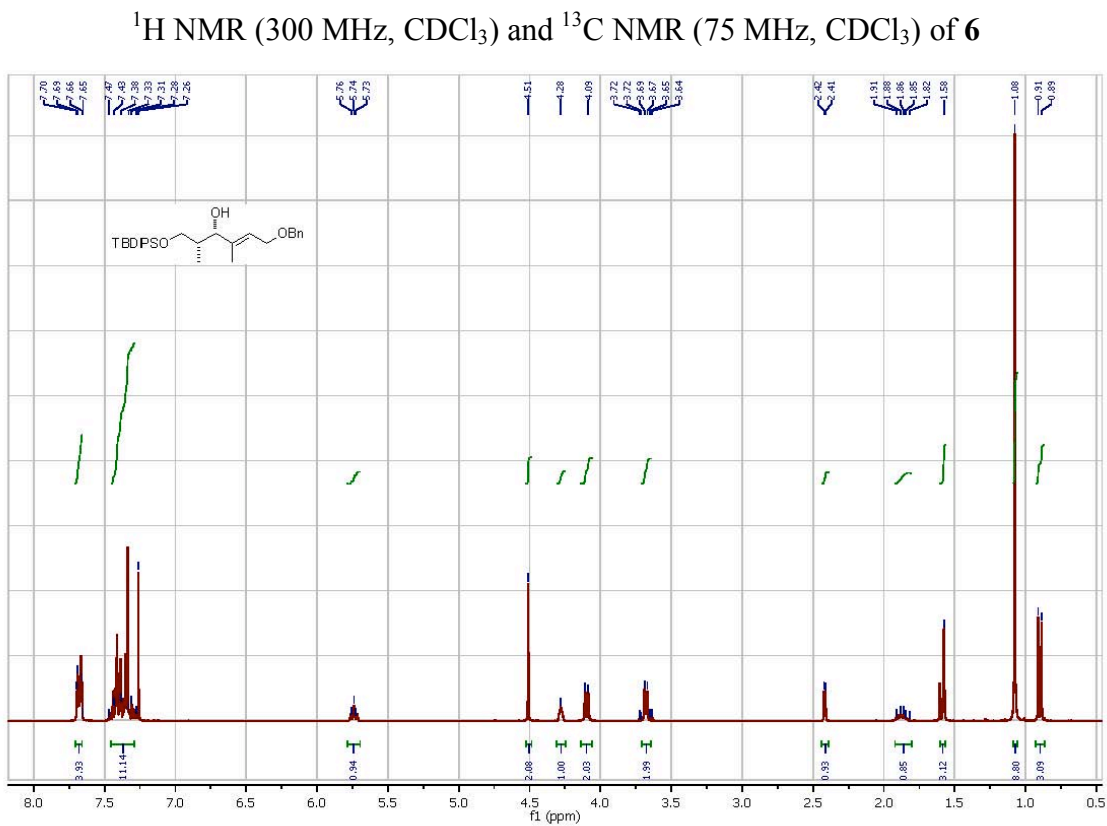


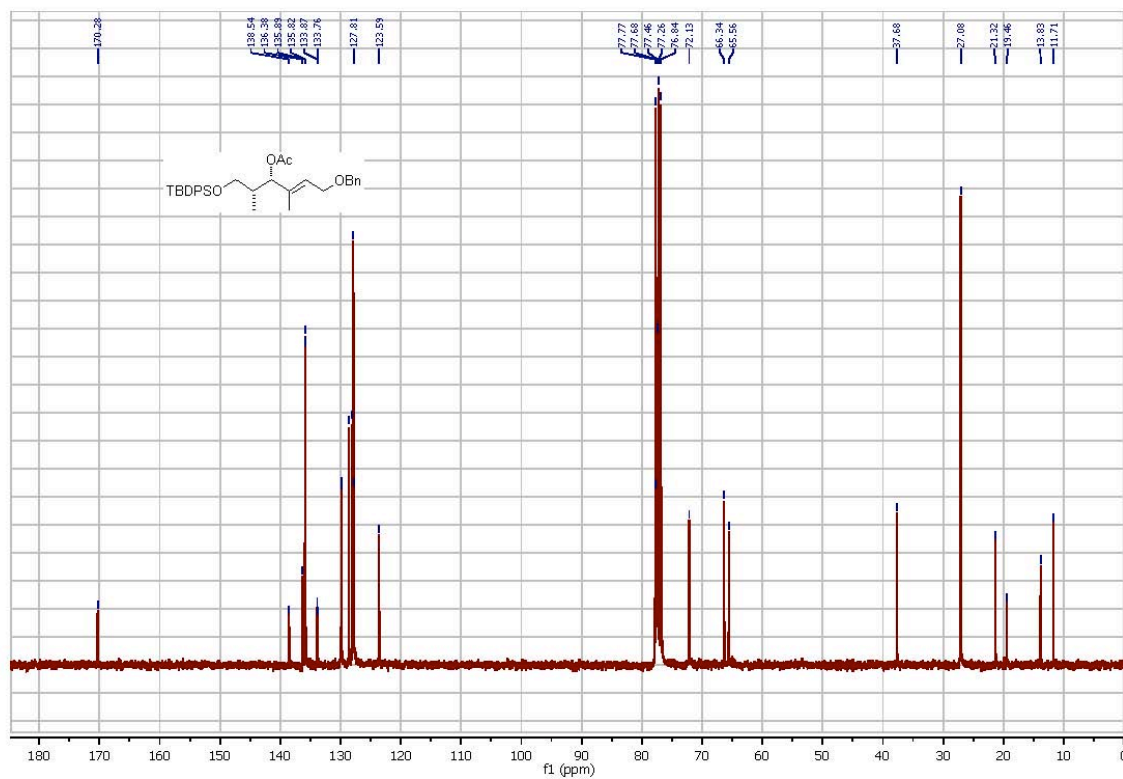
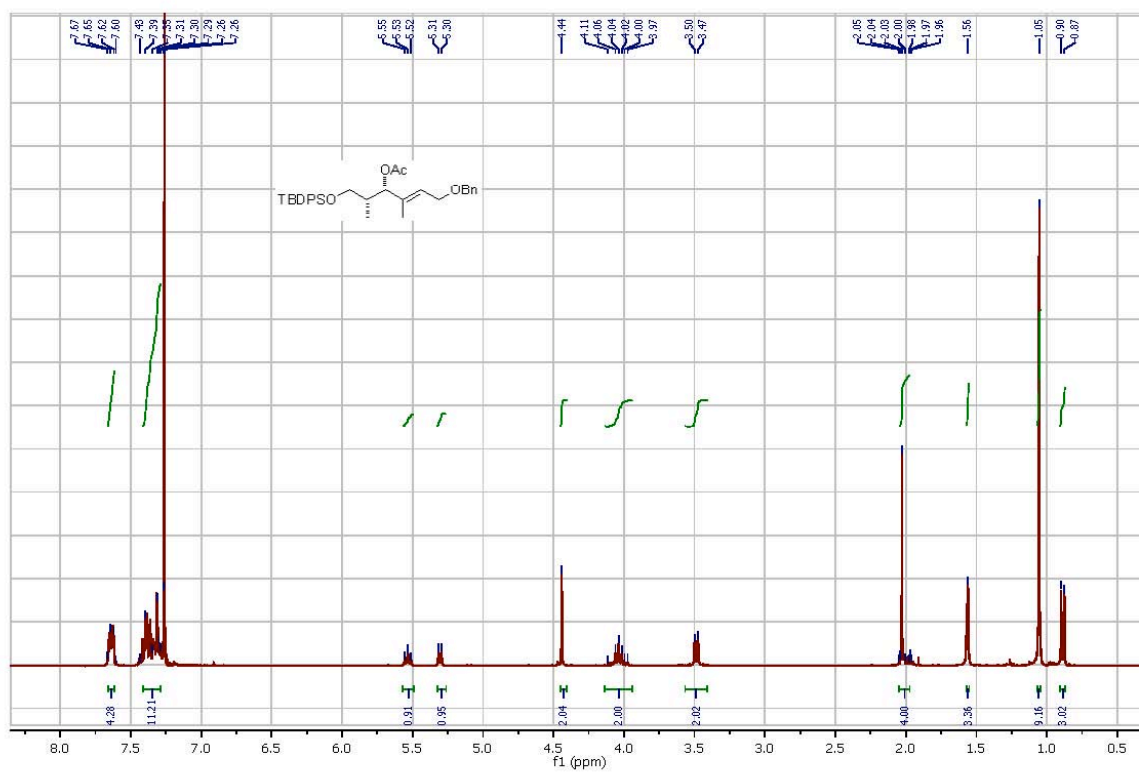
¹H NMR (300 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) of **2**

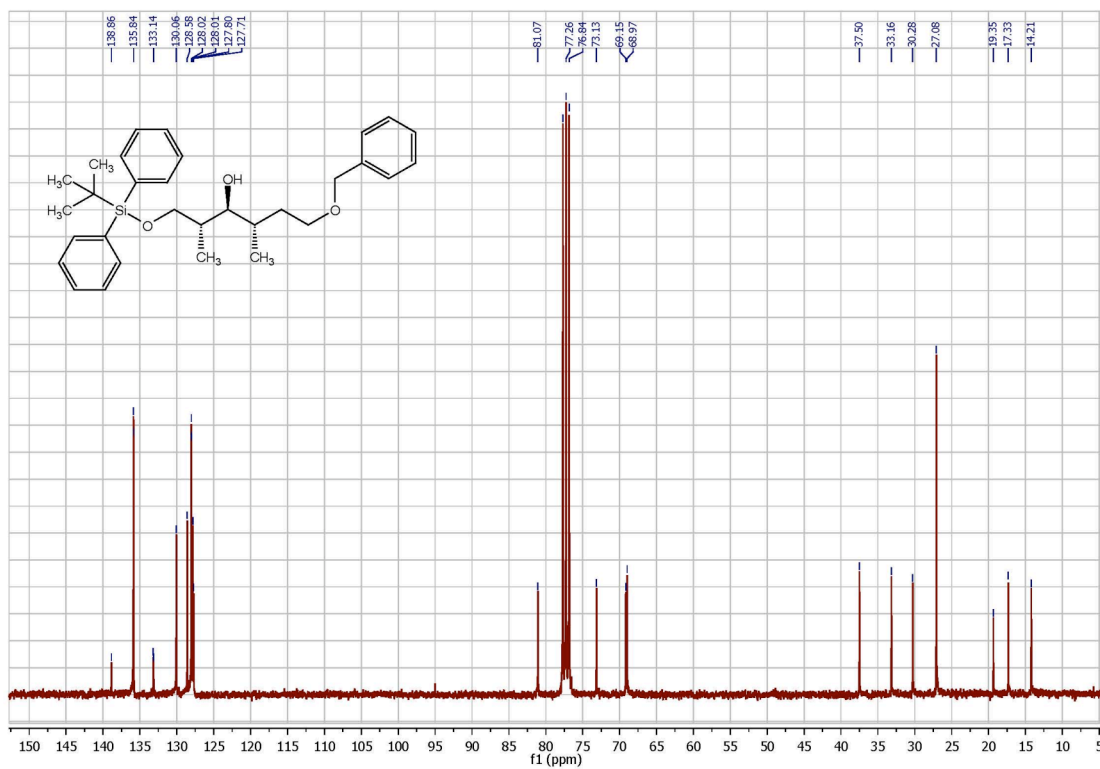
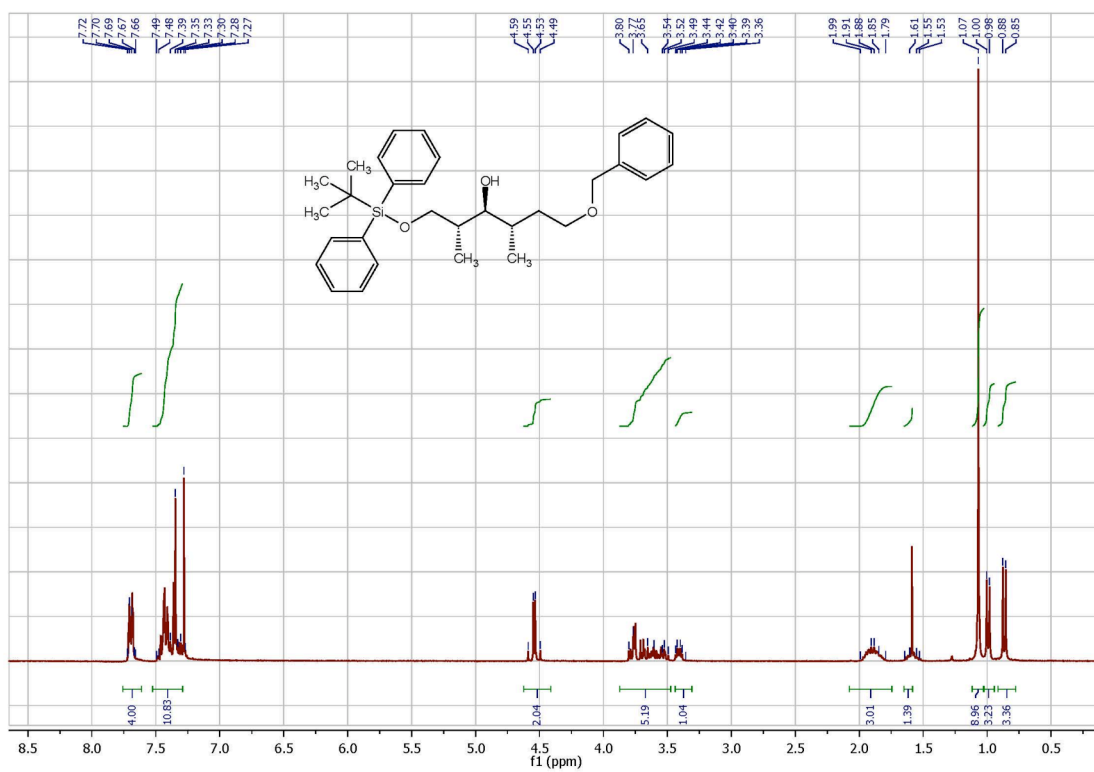
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **3**

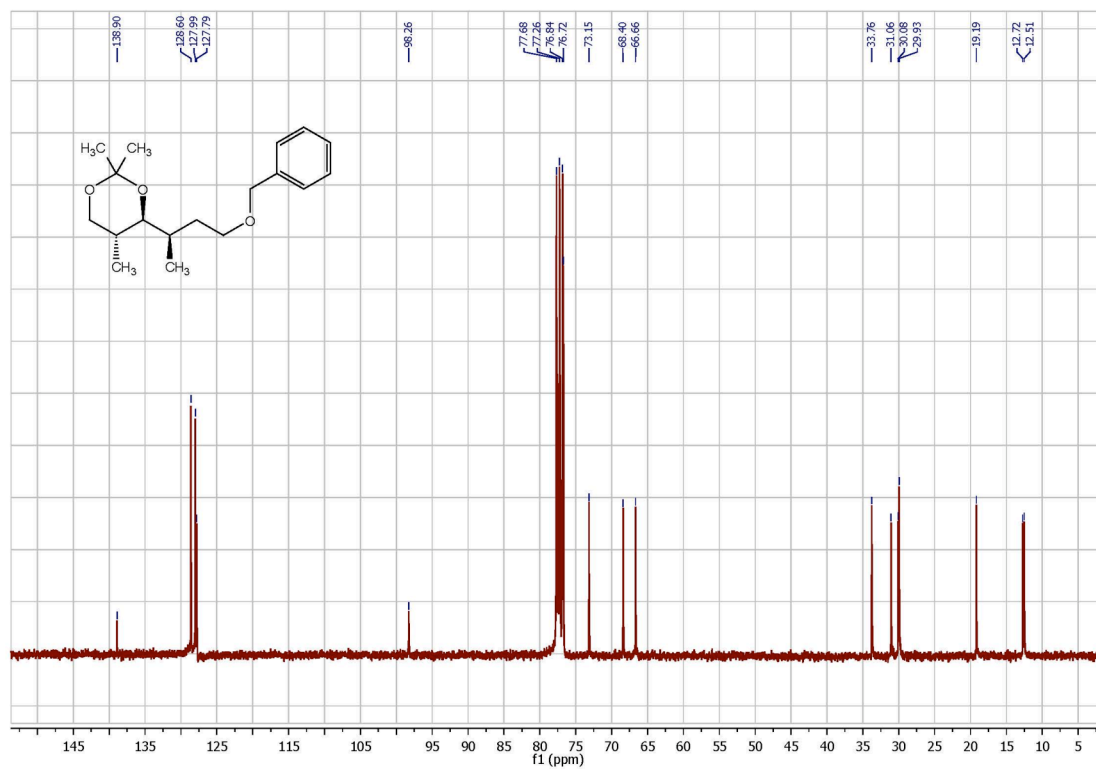
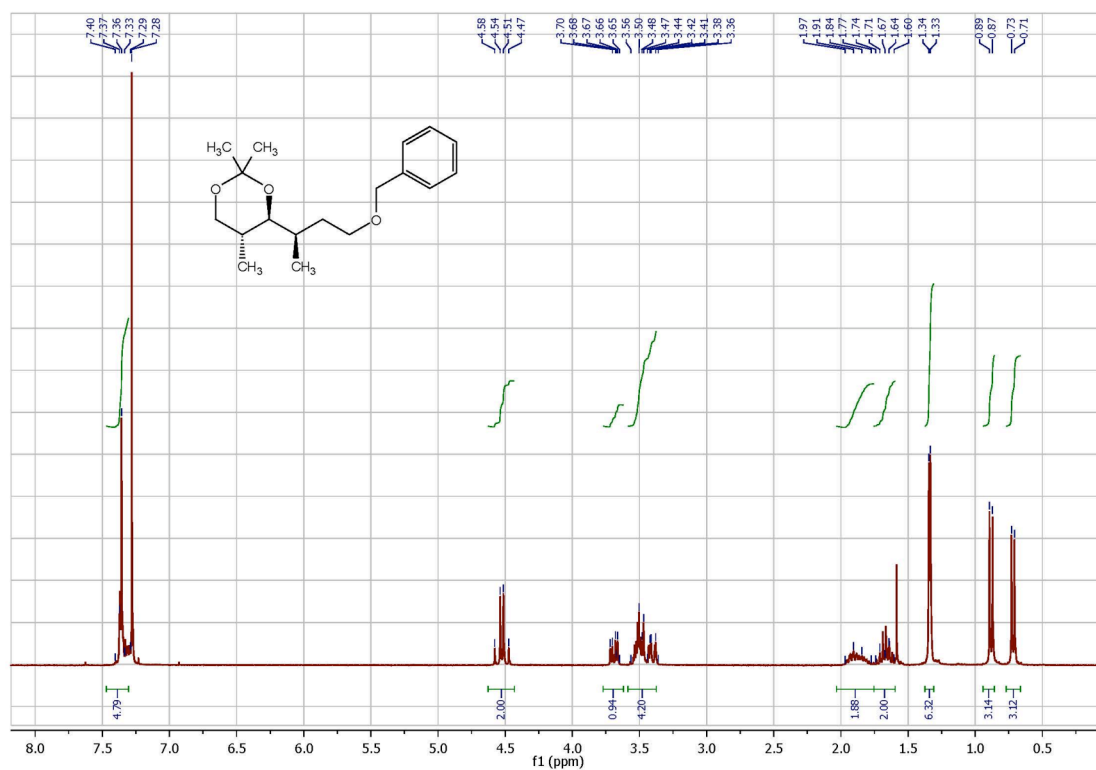
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **4**

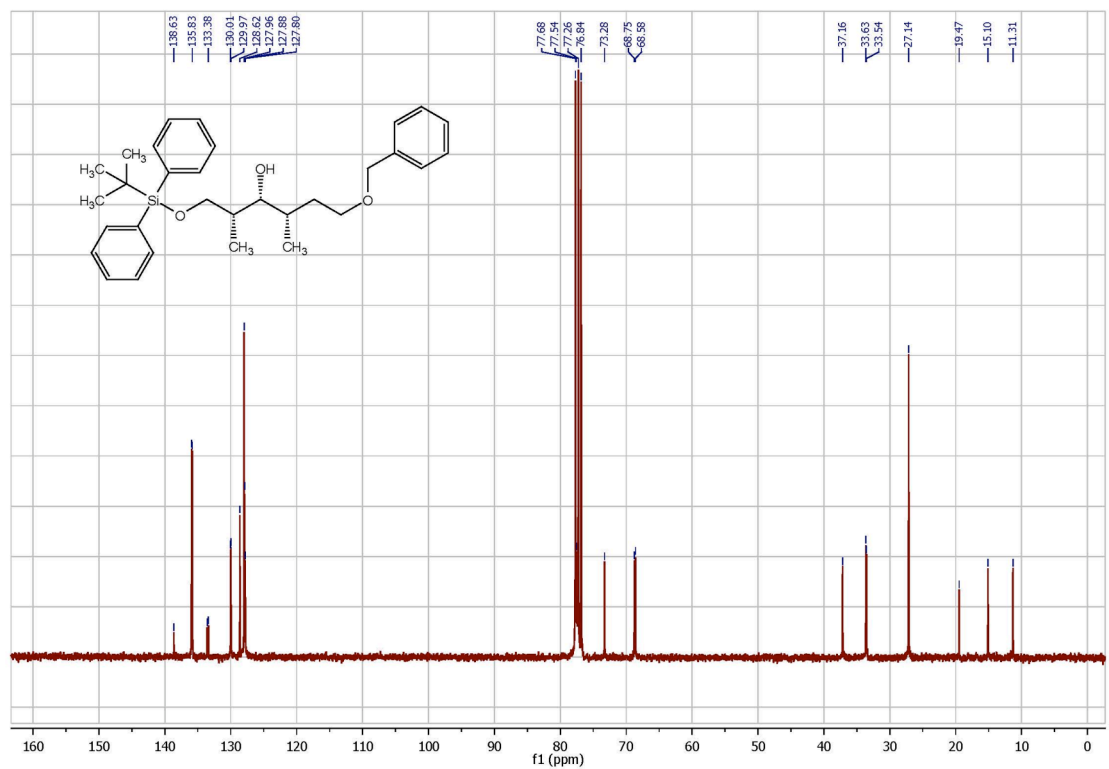
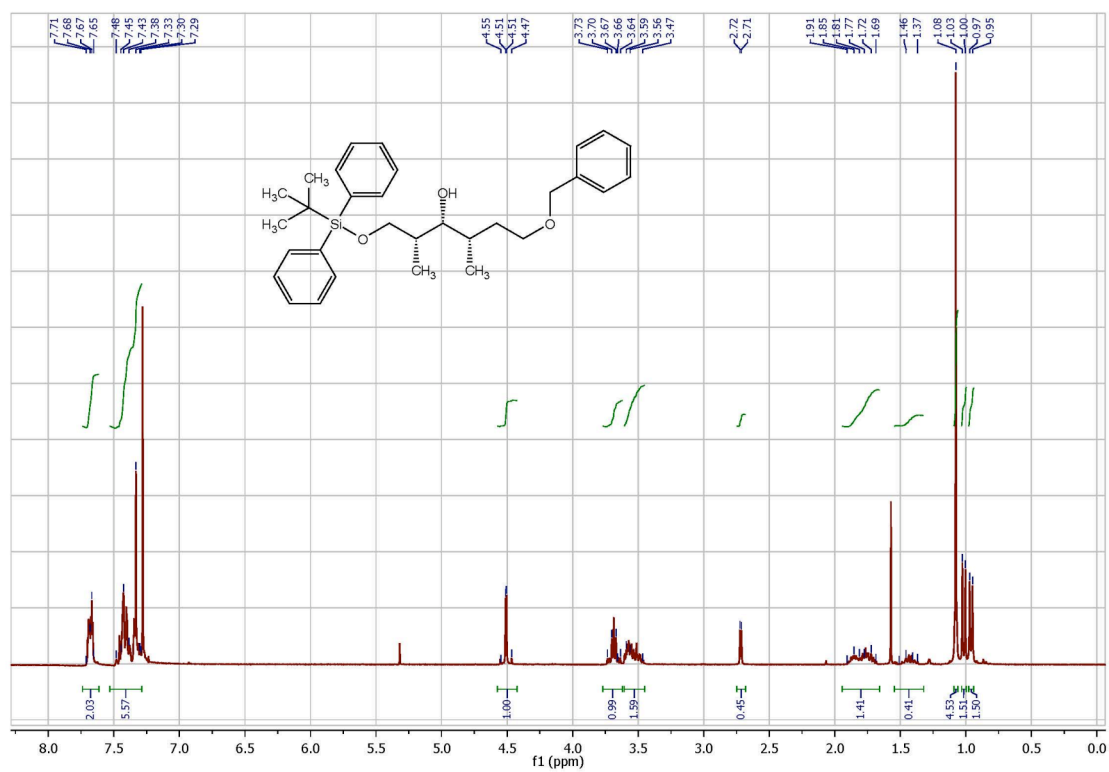
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **5**

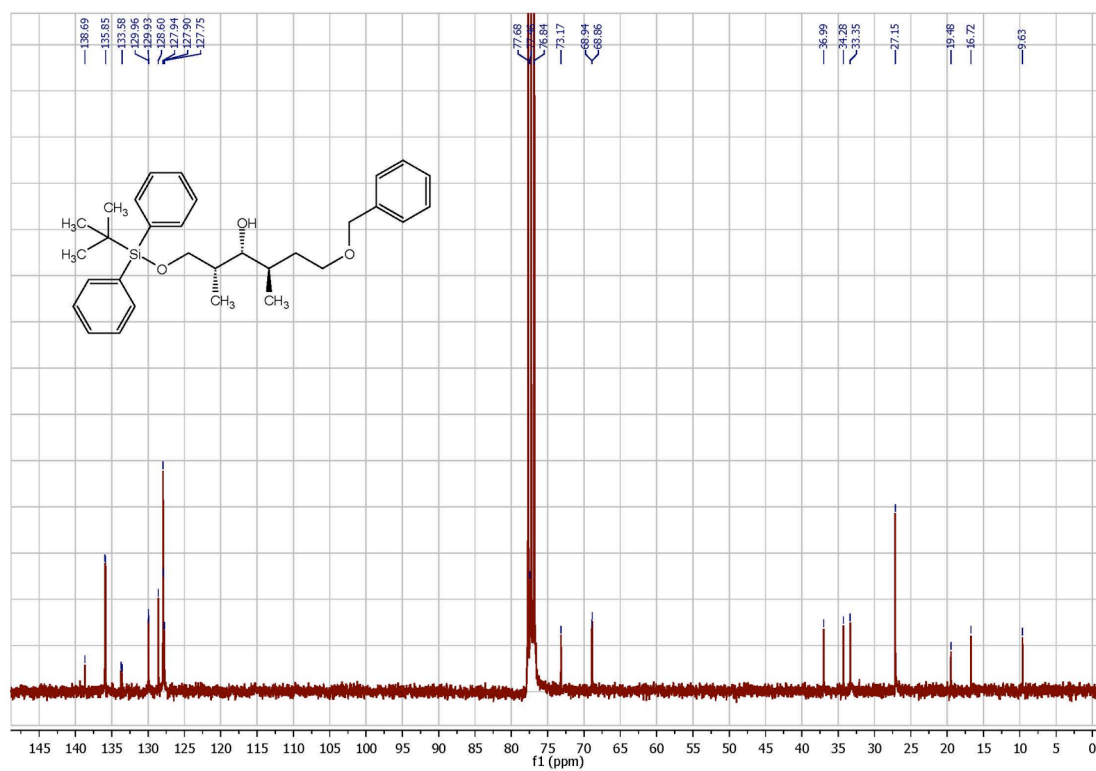
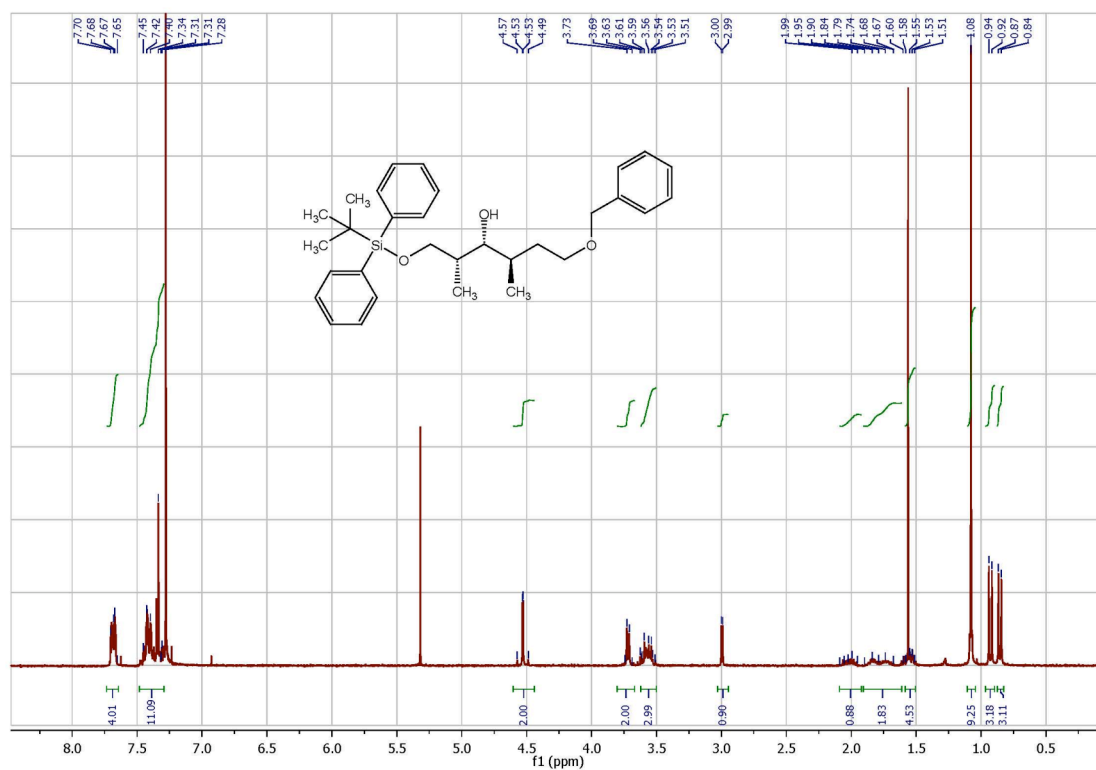


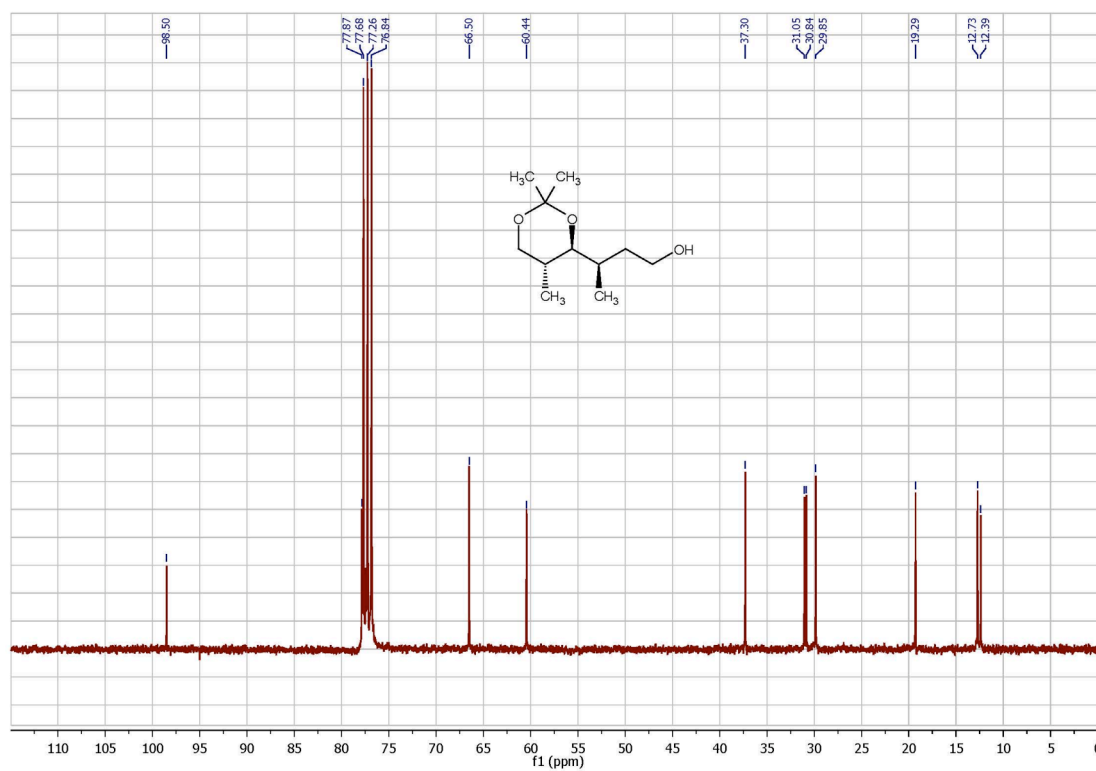
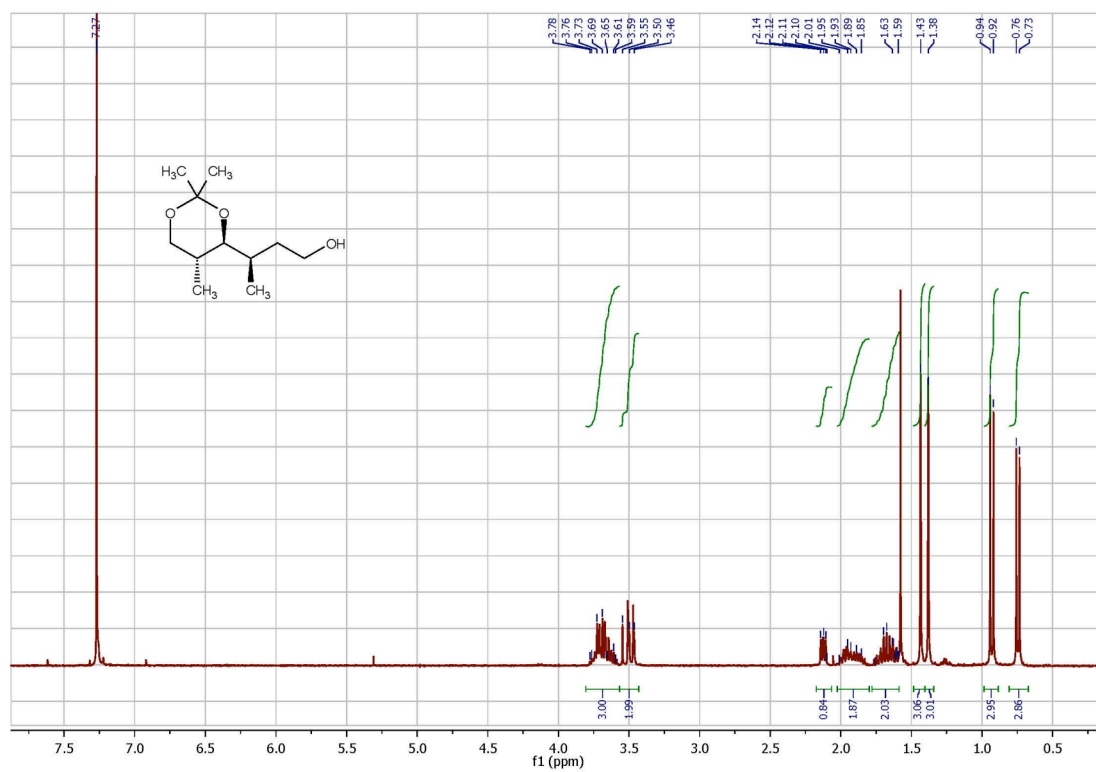
¹H NMR (300 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) of **7**

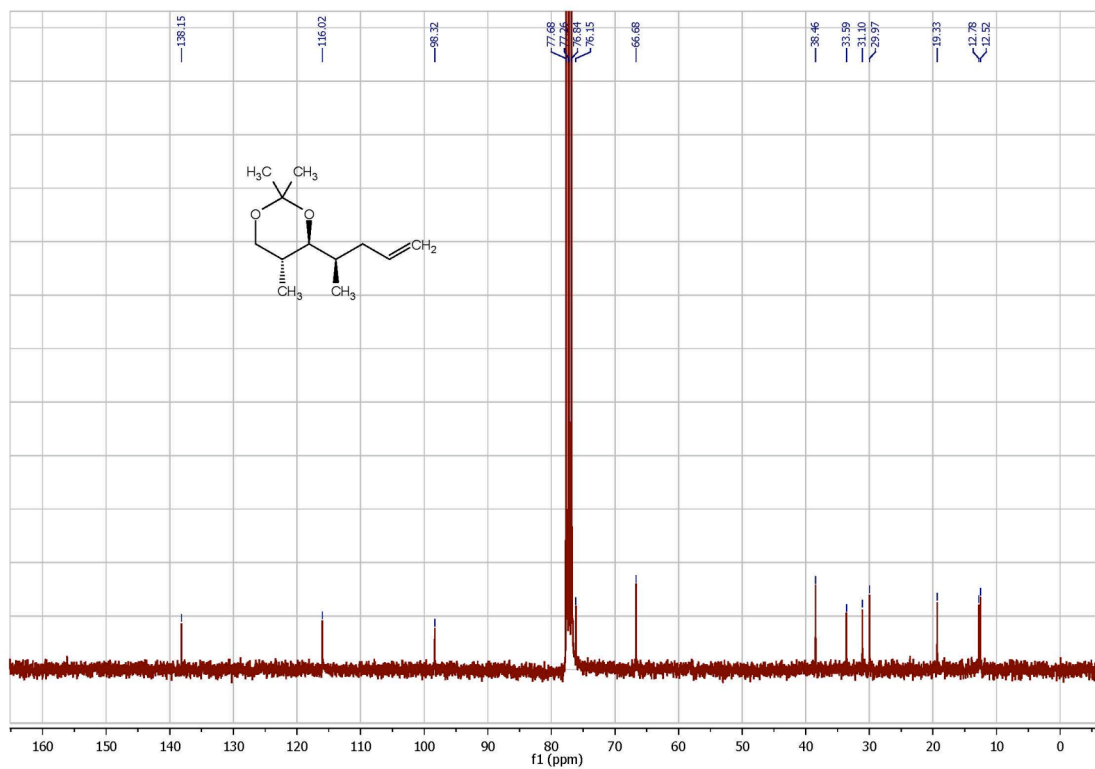
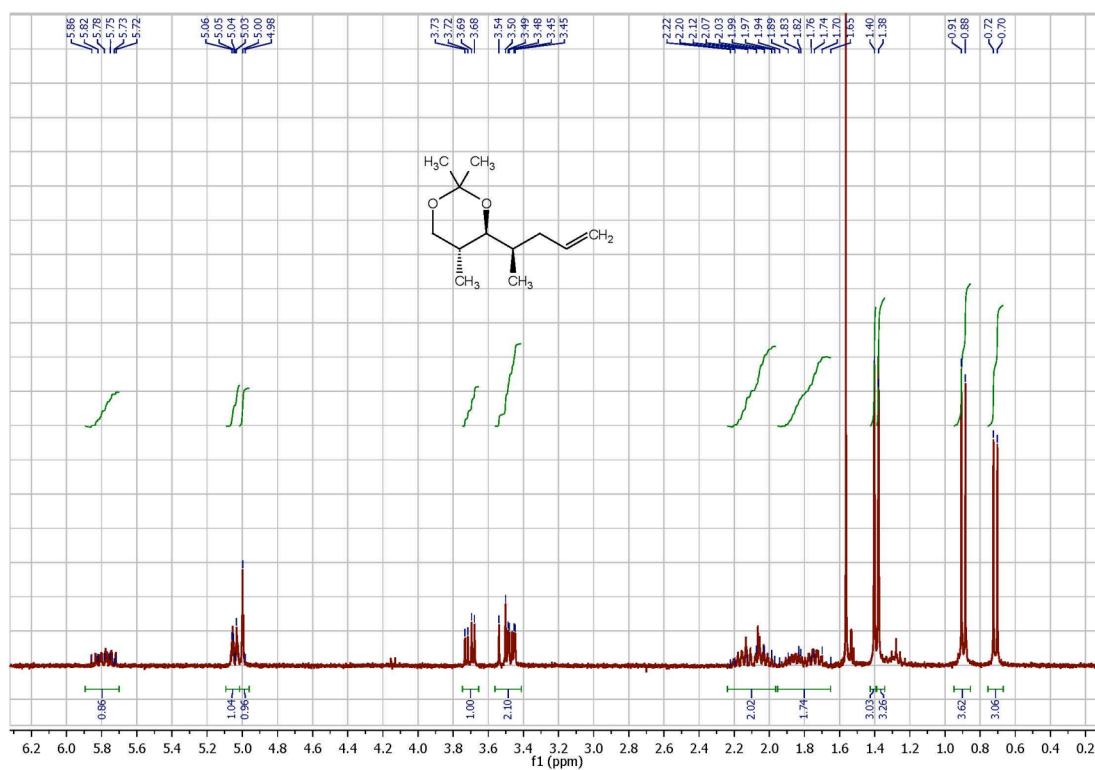
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **8**

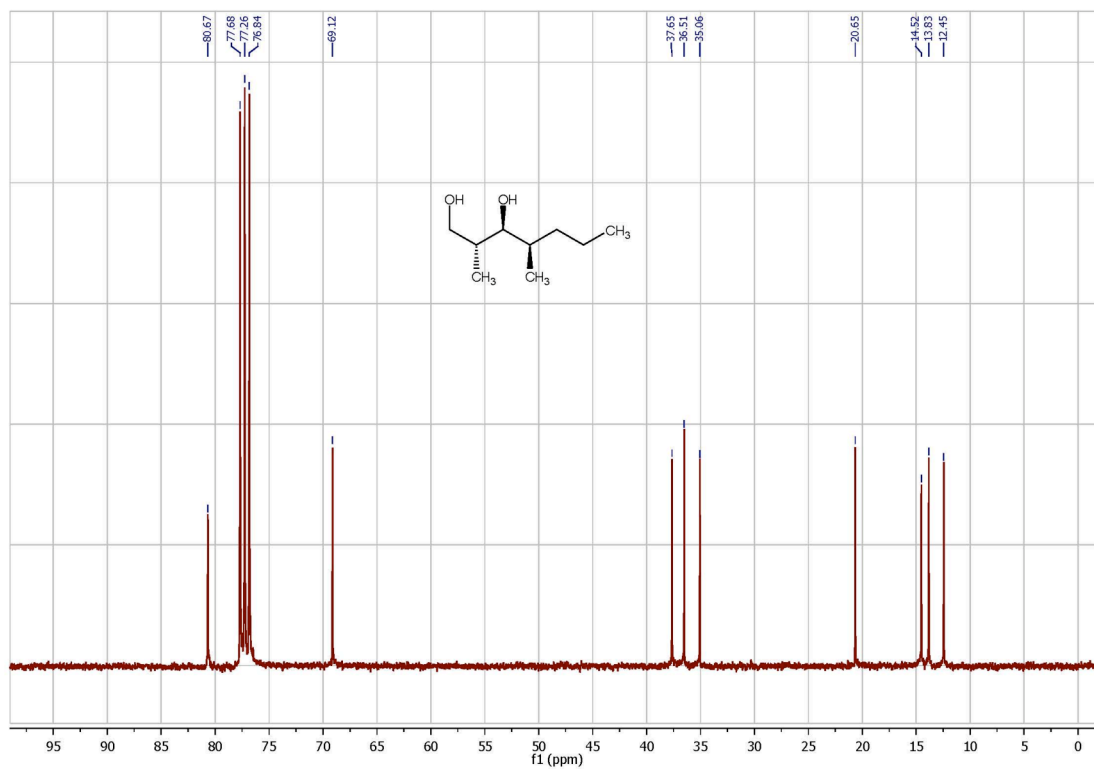
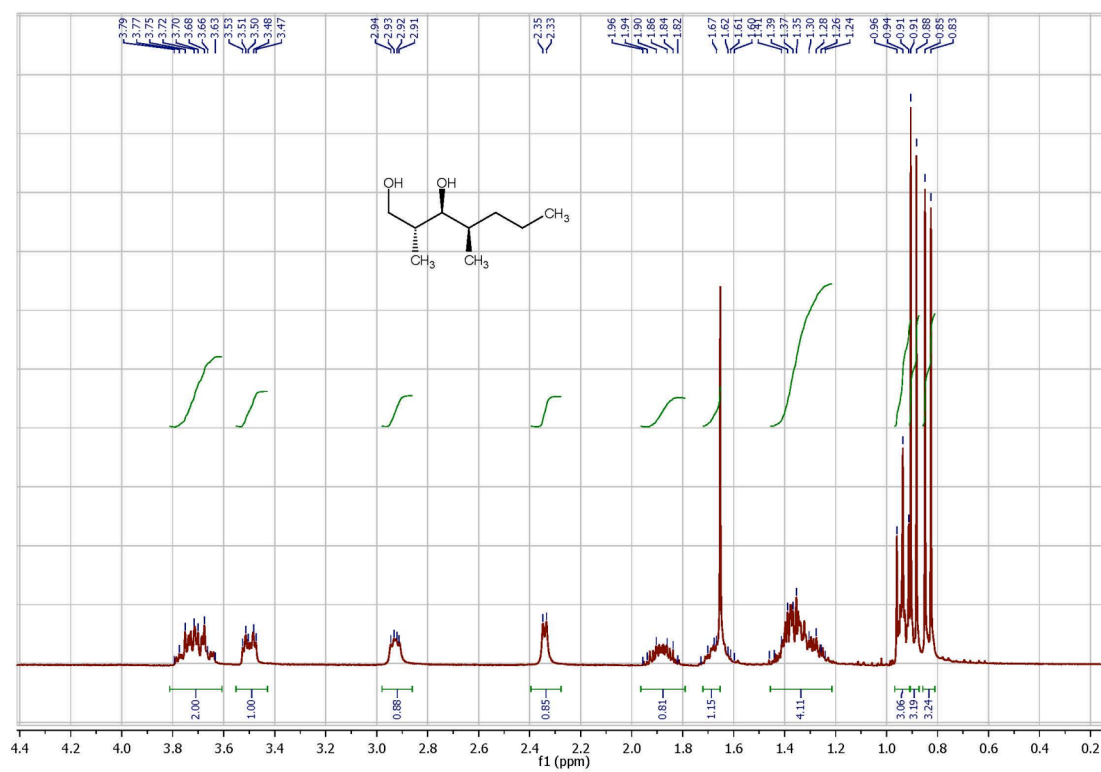
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **9**

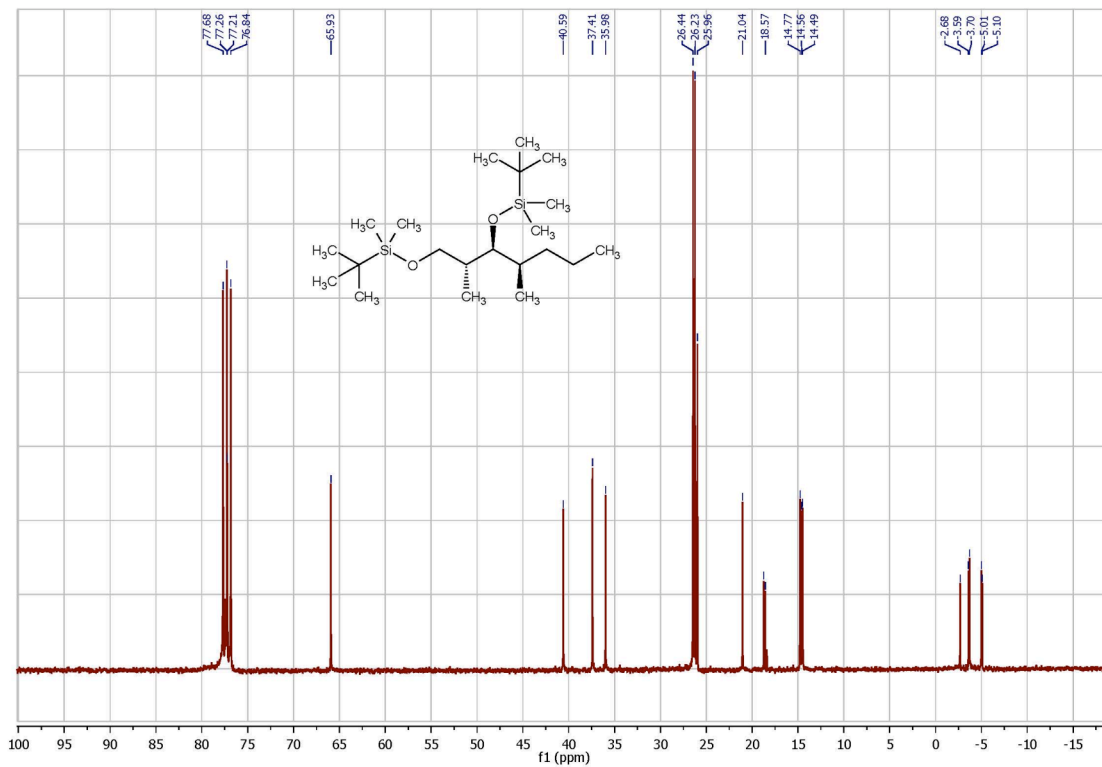
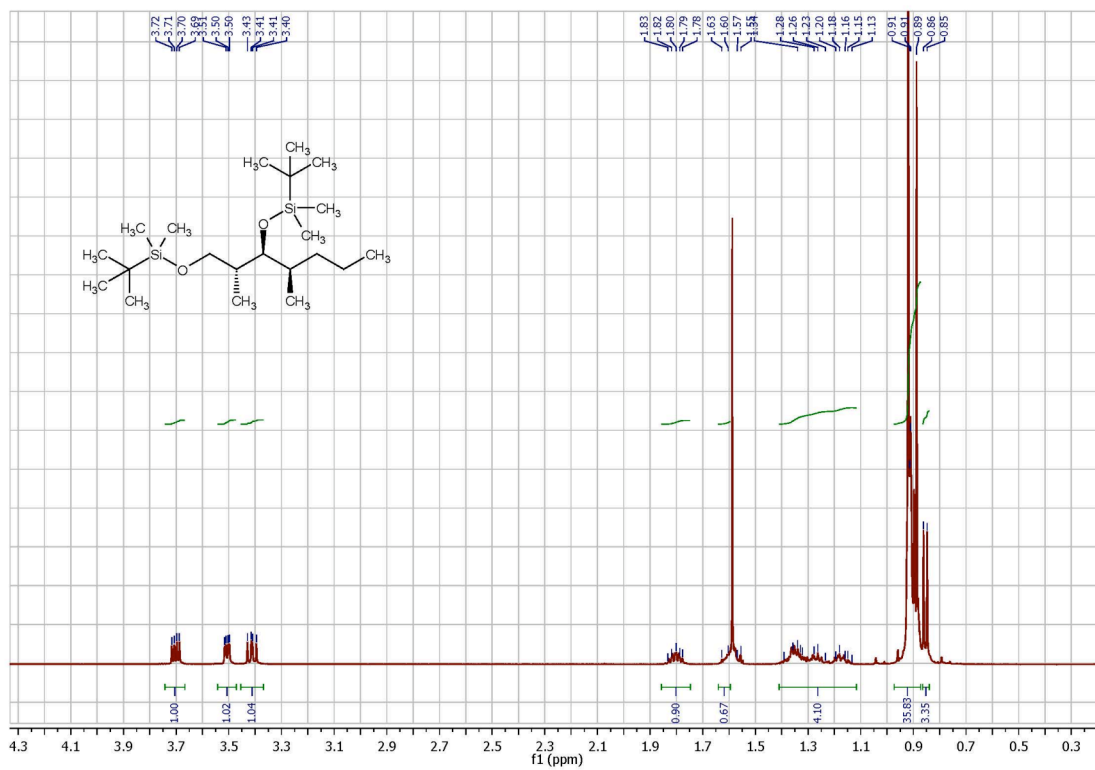
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **10**

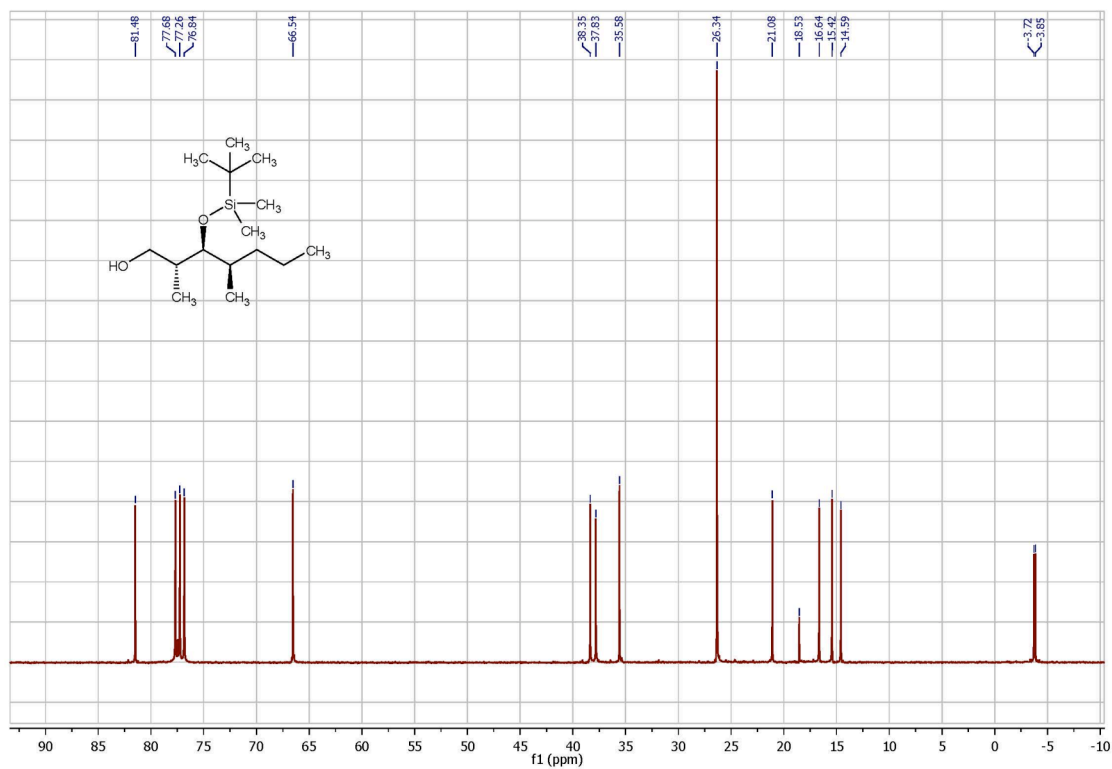
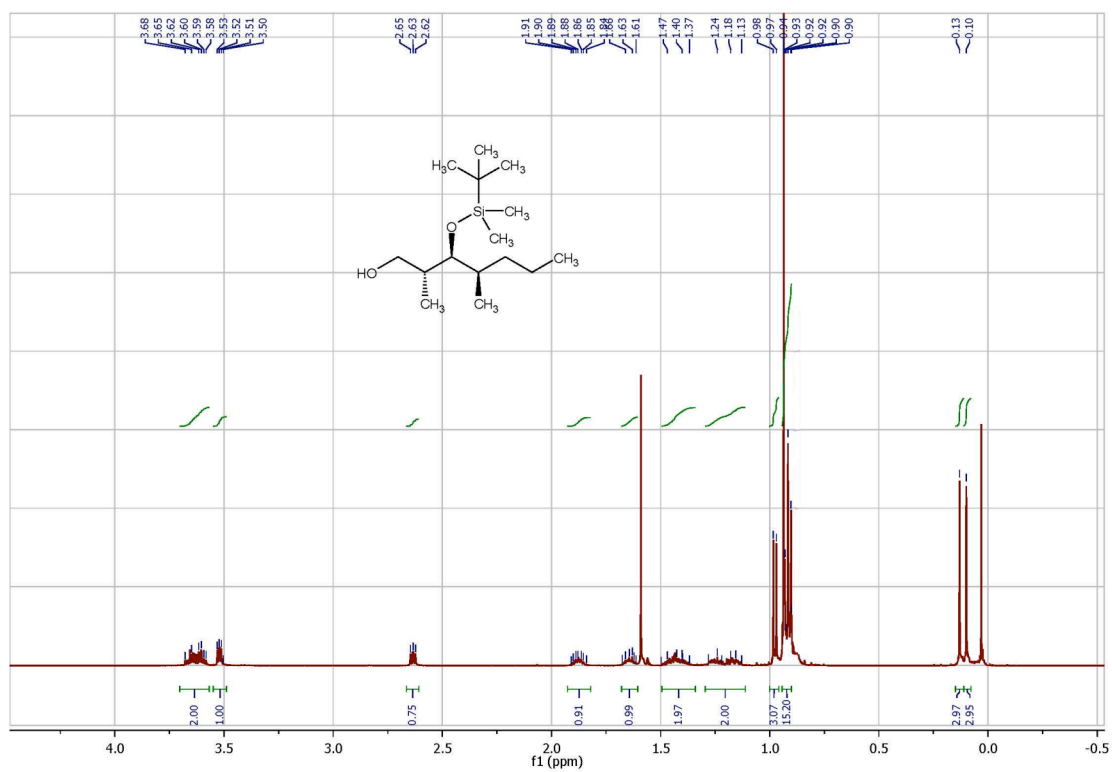
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **11**

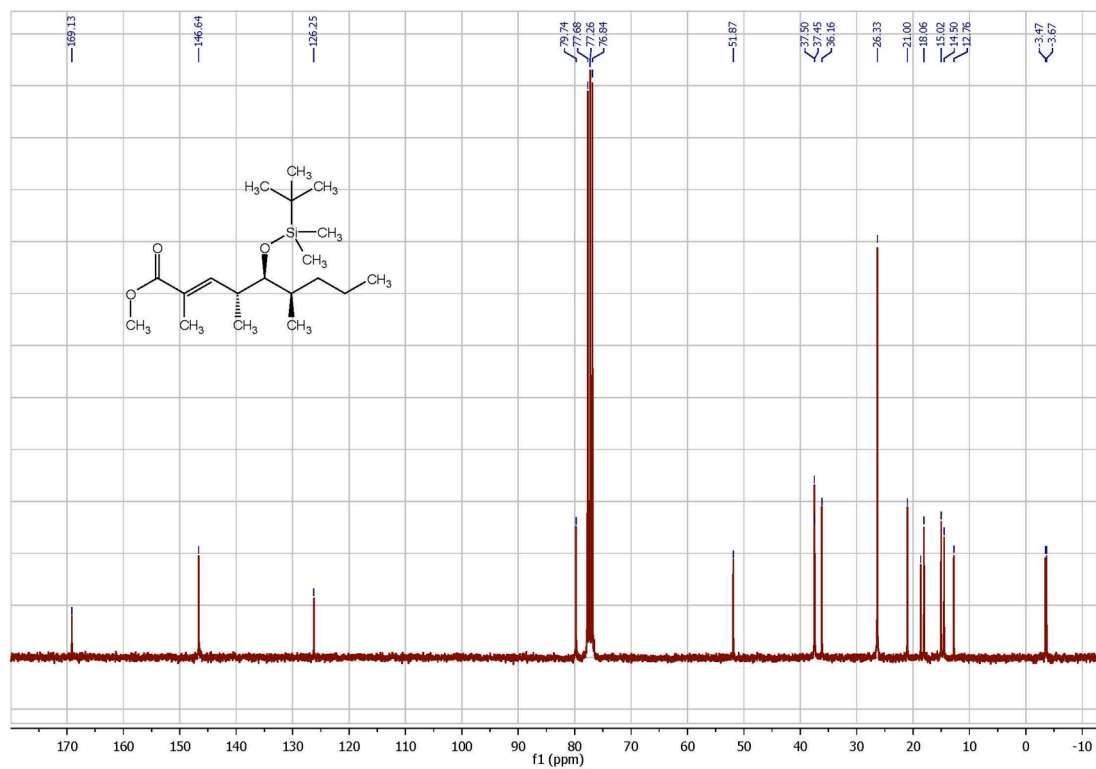
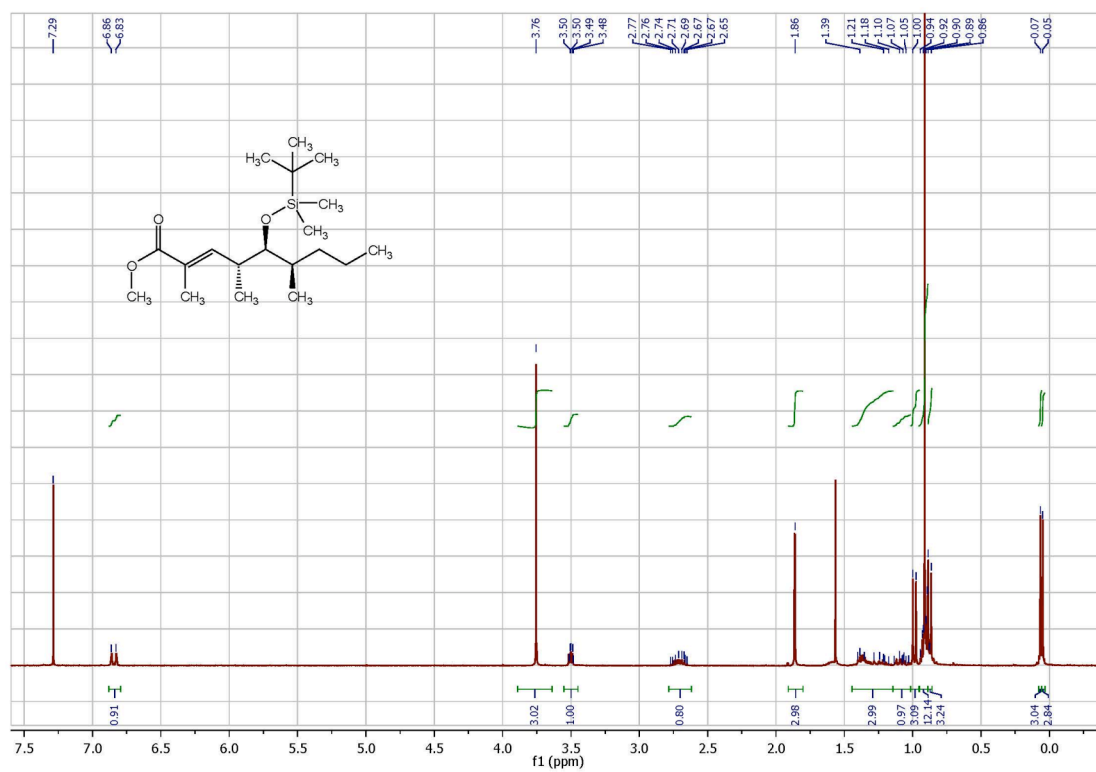
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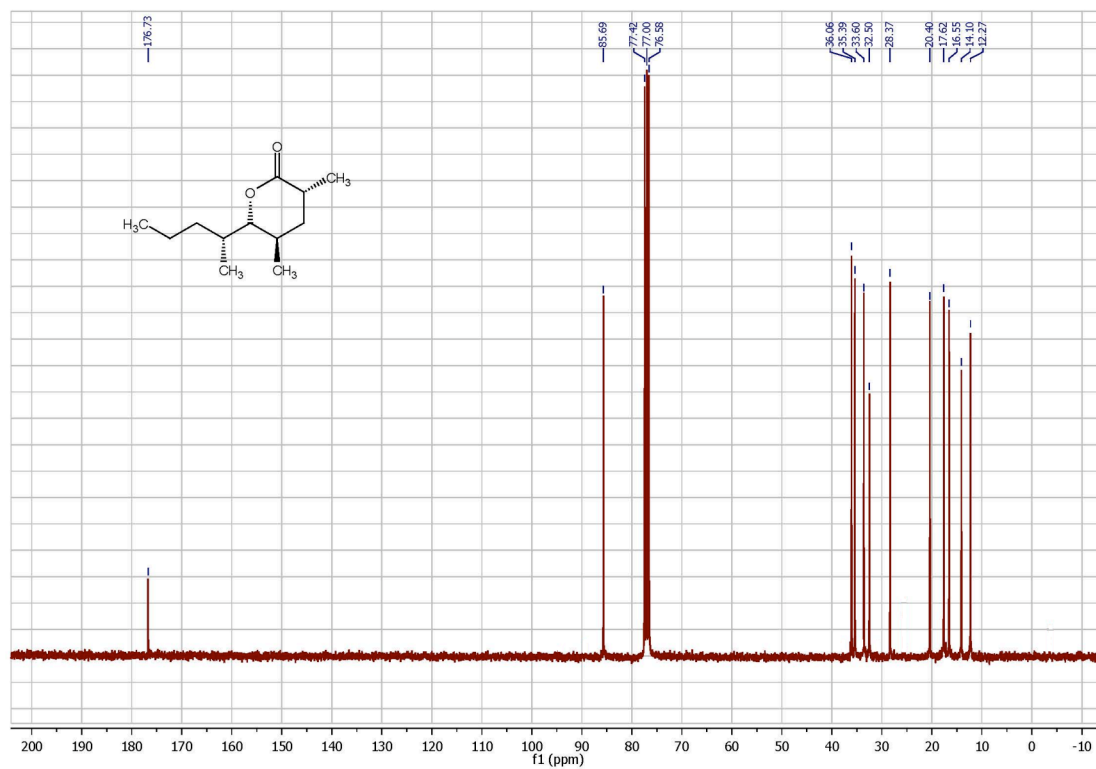
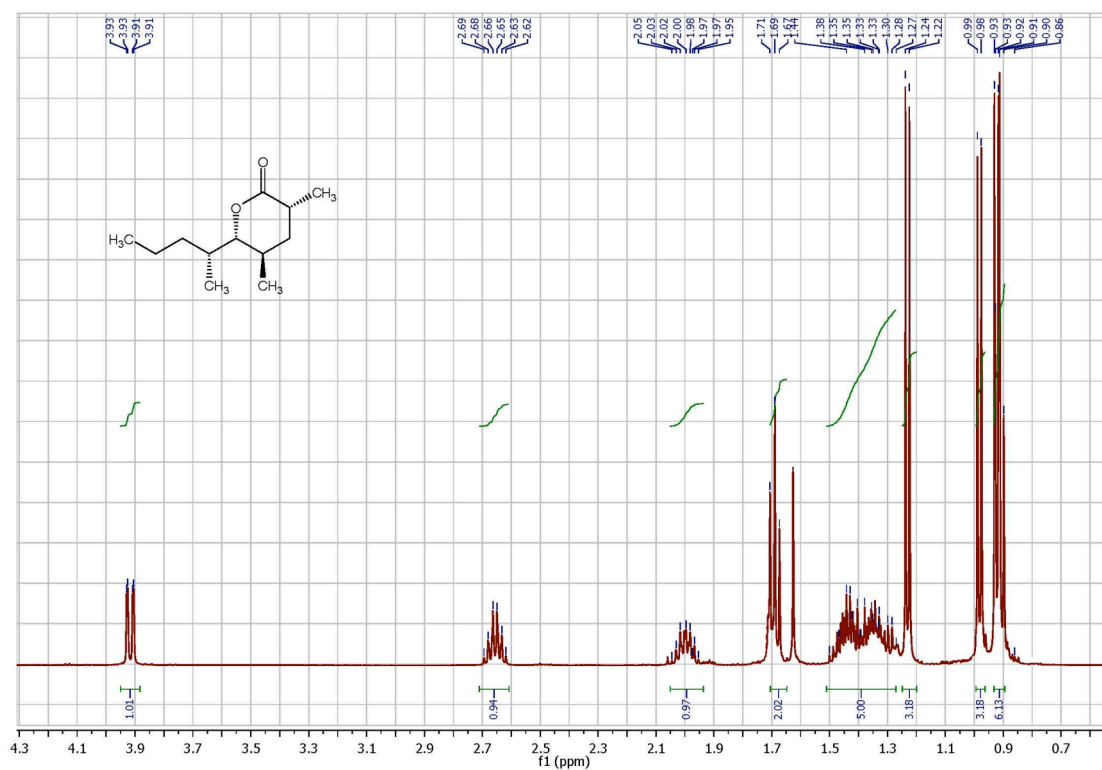
^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **13**

^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **14**

¹H NMR (500 MHz, CDCl₃) and ¹³C NMR (75 MHz, CDCl₃) of **15**

^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **16**

^1H NMR (300 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of **18**

^1H NMR (500 MHz, CDCl_3) and ^{13}C NMR (75 MHz, CDCl_3) of (-)-**invictolide**


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- (2) Díez-Martin, D.; Kotecha, N. R.; Ley, S. V.; Mantegani, S.; Menéndez, J. C.; Organ, H. M.; White, A. D.; Banks, B. J. *Tetrahedron* **1992**, *48*, 7899-7938.
- (3) Chen, Y.-H.; McDonald, F. E. *J. Am. Chem. Soc.* **2006**, *128*, 4568-4569.
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